ANNALS *of* SURGERY

Vol. XCVI OCTOBER, 1932 No. 4

TRANSACTIONS

OF THE

AMERICAN SURGICAL ASSOCIATION

MEETING HELD IN NEW HAVEN, CONN., MAY 16, 17 AND 18, 1932

ADDRESS OF THE PRESIDENT

SURGERY OF THE SYMPATHETIC NERVOUS SYSTEM

By Charles H. Mayo, M.D.

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In recent years there has been, on the part of certain investigators, an awakening of interest in the sympathetic nervous system, especially in its relation to diseases and functional disability of the tubular viscera, the glands, and the circulation.

Just two hundred years ago the term "sympathetic" was applied by Winslow to the system of ganglionated nerves. At that time, it was considered that these nerves did not supply skeletal or striated muscles other than the heart, but that they did supply the intestines and glands. In the study of some apparently new problems we often make progress by reading the work of the great men of the past, and I quote a few lines from John Hunter, the great anatomist, which were written in 1776, when we won what we thought was freedom, but Congress was unknown then:

"If it is asked why the involuntary parts have nerves at all, the answer may be given that it is not for their common actions, but to keep up the connexion between the whole, for without them an animal would become two distinct machines, and one might be acting very contradictorily to the other; but by the intercourse between will and voluntary parts, between the voluntary and involuntary, and also between these last and the mind, an universal and uniform agreement or regulation is kept up, which communication produces one kind of sympathy."

In 1800, Bichat introduced the term "vegetative" nervous system. In 1851, Claude Bernard, in his study of the physiology of the nerves to the extremities, which naturally included the gray rami of the sympathetic system, showed that section of the nerves led to dilatation of the vessels, and that stimulation of the peripheral ends of the nerves led to their constriction. We know now that vascular tonus is controlled by the gray rami communicantes which connect the sympathetic system to the somatic nerves. Gaskell, in

1886, described the regions of origin of nerves of sympathetic function as cranial, thoracic, lumbar, and sacral. The cranial outflow (principally in the vagus nerves), and the sacral outflow, or pelvic nerves, are described by most authors as parasympathetic nerves; they control normal peristalsis and occasionally reverse peristalsis. The thoracicolumbar, or sympathetic, outflow delays or brakes progress by prolonged contraction. In 1898, Langley suggested the term autonomic system, to include both sympathetic and parasympathetic outflows. The cervical sympathetic nerves very largely exert their control in the thorax. The thoracic sympathetic nerves exert their influence in the abdomen, and by connection with the aortic plexus even in the pelvis. The sympathetic nerves for the pelvis branch out from the lumbar ganglia, and supply the pelvic portion of the colon, the bladder, and certain of the genital organs.

I may remind you here that the vegetative nervous system is largely the primitive nervous sytem, which regulates and controls the fundamental structures of the earliest forms of animal life and has been left in charge throughout all evolutionary progress. Disturbance of function of the sympathetic nervous system undoubtedly is often due to mistakes made by the cerebrum in matters of food and drink and bodily care, in addition to those disturbances caused by acute and recurring infections. Fortunate, indeed, is he who learns what foods or fluids cause unpleasant reactions of the skin, such as eczema, urticaria, and angioneurotic œdema, or which cause upsets of the stomach and intestines, or disturbances of the heart and blood-vessels. If we learn it at all, most of us learn of our special internal allergy too late to obtain much relief from circulatory troubles, or from the secondary diseases that result from spasm of smooth muscle within the body. A simple one is diverticula of tubular structures.

The sympathetic nervous system has control of approximately 75 per cent. of the energy expended by the body. We are now in a position to appreciate the benefit of having our bodies managed by the sympathetic nervous system, and we are beginning to appreciate the difficulties of readjustment of function, after pathological derangement of sympathetic nerves, or of hormones the "fluid nerves," elaborated by glands. We find that the latter often have a major relationship to disease, and are subject to derangement through such mental influences as worry, overwork, lack of rest and sleep, overeating, starvation and partaking of food and drink which are toxic or especially allergic to the individual.

THE SURGERY OF THE SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system always has fascinated me. My attention was called to it again particularly in 1924, by the visit to this country of N. D. Royle and the late John Hunter, of Sydney, Australia; they presented most interesting considerations concerning the newer findings related to anatomical and physiological functions. The contributions of these men, added to what was already known of the sympathetic nervous system, opened

many avenues of investigation. I had learned of the researches of Royle and Hunter through the reports of W. J. Mayo, who, with Franklin Martin, visited Australia and New Zealand in the spring of 1924; in his comments on his visits to various medical clinics he expressed special interest in the work of Royle and Hunter.

Hunter and Royle thought that muscular tonus was a function of the sympathetic system. To support their views they made many experiments on animals, and even on birds; they found that when an animal was decerebrated, the resulting rigidity was less in a limb which had been previously sympathectomized. Royle applied this observation to cases of rigidity following war wounds of the central nervous system, treating them by ramisectomy of the brachial or lumbar rami communicantes, and he reported encouraging results. Unfortunately, this early promise has not been confirmed by the majority of workers in this field; Orbelli has expressed the view that any effects seen after sympathectomy may be ascribed to metabolic changes, mediated by the sympathetic system, in blood supply of muscle. But whatever the ultimate judgment on Hunter and Royle's operation for spasticity, the stimulating influence of their work entitles them to great respect.

Early Sympathetic Operations.—Jaboulay, in 1898, expressed the belief that pain in the lower part of the urinary tract passed to the spinal cord over the sacral rami communicantes, and he relieved some patients by ramisection made with difficulty and uncertainty by the posterior route, after resection of the coccyx. Jaboulay and Jonnesco, in 1906, popularized surgery of the cervical sympathetic ganglia for relief of exophthalmic goitre, especially for reduction of exophthalmos, and for the relief of epilepsy and angina pectoris. In this period, I removed the superior and middle cervical ganglia from several patients with hyperplastic thyroid glands and extreme exophthalmos. The operation reduced the size of the pupils of the eyes, and caused drooping of the upper eyelids, so that more of the cornea was covered and the retinal vessels were dilated, a picture known as Horner's syndrome; however, it did not seem to cause as much general benefit as did operations on the thyroid gland.

More than twenty years ago I started operating on the cervical sympathetic ganglia of patients with epilepsy, to increase the blood supply to the head. Following the method of Jaboulay and Jonnesco, I operated on a number of patients in two asylums for the insane, where patients with epilepsy are so commonly found. In some cases following operation the interval between attacks was prolonged, and in a number of cases the attacks were lighter, but I did not believe the results justified my applying the treatment to patients with epilepsy seen in general practice. We now know that the operative procedures did not extend low enough to increase the circulation to the head.

At about the same period, to relieve angina pectoris in two patients, I removed the superior and middle cervical ganglia, and also branches extending

to the lower cervical ganglion. In the second case, in addition to sympathectomy, I removed a cyst which I found in the angle of division of the right common carotid artery, and which I believed to be a cystic carotid body. In the first case, there resulted relief, graded at 50 per cent., from the severe anginal pains, and in the second there has been complete relief now for more than twenty years. At this time there is some enlargement of the aortic arch, but the patient is in his seventy-third year.

Recent Advances in the Surgery of the Sympathetic System.—Although many investigators were working on problems related to the surgery of the sympathetic nervous system, it was not until 1924 that the new work in this field was properly appreciated by the medical profession as a whole. In that year, led by Rowntree, Brown, and Hench in clinical medicine, by Adson, Craig and Learmonth in surgery, and by Mann in experimental investigation, the clinic made rapid strides in practical application of surgery to sympathetic nerves.

In vascular diseases, the work of Claude Bernard, came to fruition in the control of diseases which cause vascular contraction and decreased flow of blood; this group includes Raynaud's disease, selected cases of thromboangiitis obliterans or Buerger's disease, and selected cases of scleroderma. The measurement of vasodilatation which follows injection of foreign proteins, for example, typhoid vaccine, has provided a means of accurately estimating the possibilities of vascular distention. Brown and Sheard have designed a thermocouple which makes it possible to measure the changes in the temperature of the skin which follow such an injection. Adson and Brown have shown that the most favorable cases for operation are those in which the rise in temperature in the skin of the extremities is three to five times the rise in general temperature of the body. It is marvellous to see the relief which follows ganglionectomy and ramisectomy in Raynaud's disease; in Buerger's disease the results in selected cases are similar, but in some cases, although the extremities are warm and free from pain, and are restored to usefulness, there are still patchy changes in color due to permanent changes in the walls of some of the vessels.

Because of its associated interest, I wish to state the essential facts concerning a music teacher (a nun), aged thirty-three years. Starting with a normal systolic blood-pressure of from 125 to 130 millimetres of mercury, she would experience a rapid rise in pressure to 300 or 330 millimetres with headaches and a great sense of vascular oppression. The attacks might last a short time, come several times a day, or continue for several hours or a number of days. The patient had been so troubled for two years. I asked permission to explore the upper part of the abdomen, because in this area are many coördinated sympathetic structures. Making a surgical exploration in this case, I found within the peritoneal cavity no pathological condition other than increased venous congestion. At the upper left side through the posterior peritoneum was felt a rounded tumor, that lay anterior to the left renal vessels and adjacent to the left suprarenal gland. The posterior peritoneum was opened and the encapsulated tumor removed. The growth had many nerve connections which were torn loose, and the operative field was extremely bloody, as the posterior peritoneal veins were very large. Bleeding was

controlled only by packing. The patient made a complete recovery and now has been well with normal blood-pressure for more than five years.

Microscopical examination disclosed hyperplastic ganglionic nerve tissue, comprising a rounded, encapsulated tumor, with cells that appeared to be of a pre-malignant type.

Search of the literature disclosed reports of five post-mortem examinations of persons who had died after prolonged sickness, with similar symptoms of sudden and often repeated rise of blood-pressure. Three of these subjects were observed in France, and two in Germany; tumors were found at necropsy, involving sympathetic nerves and ganglionic structures along the spine, in the superior and inferior (particularly the middle) mediastinum, and the upper part of the abdomen. One case was similar to the case here reported. In four cases the tumors were malignant. Were they malignant in their early development? Probably not. Today, we believe the cancer cell is a secondary development on a previously exhausted or pathological cell.

Since Rowntree and I reported the case just described, two similar cases have been studied and the patients have been operated on in this country.

Scleroderma.—Adson, Brown and O'Leary have reported a number of cases of vascular disease of the skin, in which the patients have been relieved by operations on the sympathetic system. In describing the proper selection of cases for operation, he emphasized that the lesions should be symmetrical, and that the history should suggest chronic sympathetic overactivity.

Arthritis.—In 1928, Adson and Rowntree reported the effects of sympathetic ganglionectomy and ramisectomy in selected cases of arthritis. Later Hench and Craig found that the operation was most successful among patients with cold, clammy, sweaty hands and feet, whose symptoms were much relieved by heat. Adson, Henderson, and Hench have stated that, to secure the best results, the patients should be less than thirty-five years of age, and that the arthritis should be of the periarticular type, without changes in the articular ends of the bones; in a few selected cases, in which the patient was older, improvement has also occurred.

Diseases of Tubular Organs.—A few years ago, I endeavored to relieve pyloric spasm by section and separation of the nerves and mesenteric attachment above and below the pylorus, working through a circular incision through the muscle of the stomach, an inch and a half above the pylorus. In some, the acids were not changed, in others they were low after a considerable period. I cannot predict what would occur in enough of these cases to warrant continuing the use of the method. Mann, in his experimental work, showed that in order to affect the stomach, division of the nerves must be made above the diaphragm. This fact attracts our attention to cardiospasm, and we think of pylorospasm in its relation to ulcer, and as a secondary symptom in acute and functional diseases of the digestive tract. Spasm of the sphincter of Oddi, at the outlet of the common bile-duct, is certainly related to disease of the liver and of its system of ducts, and is probably an associated factor in the development of interstitial disease of the head of the pancreas and in disease of the gall-bladder. Removal of the gall-bladder

undoubtedly frees this sphincteric spasm and it should be practiced before the secondary and tertiary states develop, in which gall-stones add their mechanical problems.

Megacolon, or Hirschsprung's Disease.—Throughout many years, we have operated on patients with megacolon, or Hirschsprung's disease. Following the reports of Wade and Royle, concerning treatment of the disease by ramisectomy, Judd and Adson at the clinic performed lumbar ganglionectomy and trunk resection in such a case, and secured complete relief; later they operated successfully in other cases. Morton and Scott, of Rochester, New York, proposed the use of spinal anæsthesia in selecting cases for operation; by interposing this temporary block between the bowel and the spinal cord the probable result of sympathectomy could thus be tested, and those cases in which evacuation of the bowel followed spinal anæsthesia could be chosen for operation.

Learmonth and Markowitz showed that the nerves in the pelvic mesocolon of the dog actively inhibit movements of the bowel, and that section of these nerves increased colonic peristalsis; they also showed that the internal anal sphincter is contracted by the action of sympathetic nerves. Applying these findings to man, Rankin and Learmonth have operated in a number of cases of megacolon; they have applied neurectomy to the pre-sacral nerve and the inferior mesenteric nerves; the results have been very satisfactory.

After division of the extrinsic nerves to relieve megacolon, there need be no fear of a paralyzed intestine, because the tubular viscera have intrinsic innervation which can be stimulated or depressed from without, just as the heart has the bundle of His. Alvarez has shown that the small intestine has so strong an innervation that if the intestine is removed from the body and kept in an ice-box for thirty-six to forty-eight hours, and then placed in warm Ringer's solution, it will start movement of the fluids within it, by peristaltic action, in the normal direction.

Urinary Retention.—Learmonth has shown that the pre-sacral (sympathetic) nerve causes relaxation of the bladder and closure of its outlet; in the presence of a weakened detrusor or motor muscle, and a great amount of residual urine, he has secured, by resection of the nerve, complete voluntary emptying of the bladder in four cases. Such conditions as those which Learmonth has relieved may arise from injury or severe infections in the lower part of the spinal cord, which reduce but do not wholly destroy the power of the pelvic nerves that are in control of evacuation.

In 1913, Latarjet and Bonnet made accurate dissection of the nerves to the lower part of the urinary tract. In 1921, Rochet published a paper in which he distinguished three kinds of pain in this region: (1) Lower ureteral colic; (2) painful contraction of portions of the bladder, and (3) pain due to lesions of the vesical sphincter. Impulses of pain arising from these causes are carried to higher levels of the spinal cord through white rami communicantes, which hook up the sympathetic system with somatic nerves. By section of nerves we may relieve the pain of those suffering from tuberculosis of the

bladder and hopeless cancer. I believe, too, that operations in this field may offer possibilities of relief in cases of so-called ureteral stricture of large calibre. I presented a paper on this subject at the Southern Surgical Association meeting in December of last year, because I believe that failure of repeated dilatation in some of these cases may be due to persisting sympathetic dysfunction. Incidentally, I would state the interesting fact that during menstruation and during the first three months of pregnancy the ureters are dilated, without any dilatation of the pelves of the kidneys.

Fearing I may have disturbed the equanimity of your belief with regard to the sympathetic nervous system, I will quote Fulton, concerning Cannon, the well-known physiologist: "Normally, in the sheltered existence of a laboratory, an animal has little occasion for emergency adjustments made by the sympathetic system, and Cannon has been able to show that an animal whose entire peripheral sympathetic system has been extirpated is able to exist without difficulty so long as it is not exposed to extremes of temperature or to any other relatively severe condition which would require a struggle for existence."

Sympathetic Ganglionectomy and Ramisectomy Performed at The Mayo Clinic to May 1, 1932

Raynaud's disease	115*
Thrombo-angiitis obliterans	193†
Scleroderma	29‡
Arthritis	92§
Hypertension	4
Megacolon	13‖

* 56 of the operations for Raynaud's disease were bilateral
† 93 of the operations for thrombo-angiitis obliterans were bilateral
‡ 14 of the operations for scleroderma were bilateral
§ 46 of the operations for arthritis were bilateral
‖ 5 of the operations for megacolon were bilateral

CARCINOMA OF THE MOUTH AND TONGUE

By John Fraser, M.D.
of Edinburgh, Scotland

Carcinoma of the mouth has the interest which attaches to an always serious and often fatal disease, its pathology has many points of alluring significance, while the problem of its treatment presents many difficulties.

It is, I think, appropriate that I should introduce the subject with a reference to the incidence of the disease in Scotland. The Registrar General has kindly put certain figures at my disposal, and their summary is as follows. The population of Scotland at the present day is 4,780,000, and of that total the number of males is 2,325,867. Taking a still more selective group, that of males above the age of forty years (the period in which the great majority of tongue- and mouth-carcinoma cases occur) we find that it presents a total of 702,000 individuals. This is the field—the yield is more difficult to estimate, but this we know, that during the decade 1920–1929 a total of 3,291 persons succumbed as the result of carcinoma of the buccal cavity. This is a mortality figure; it is therefore a conservative estimate of morbidity, but it is the only accurate summation at present available. The information indicates that some 330 cases die in Scotland each year from the disease. The figure does not seem unduly large, and I have been unable to secure evidence as to how it compares with the incidence in other countries.

Pathology.—*Normal Buccal Epithelium.*—It has been my intention to treat the subject on pathological rather than on statistical lines, and therefore I would now ask you to review with me the epithelial arrangements as they exist within the cavity of the mouth.

Buccal epithelium is arranged on a uniform plan. It is true that in certain situations there are special arrangements, as we shall presently see, but the general picture presents a basis of similarity. If we examine the mouth cavity of a 35-millimetre fœtus (Fig. 1), we find that the epithelial lining is composed of a single layer of cubical epithelium. The cells are uniform in shape and in size, the cytoplasm contains a large number of granules, and the nuclei are in process of repeated mitotic division. It is from this source that the fully developed epithelium of later life is developed. By a process of division and some degree of cell differentiation an arrangement is produced by which the cell lining is grouped in four super-imposed layers.

Considering the arrangement in more detail, the deepest layer (Fig. 2) resting upon the sub-epithelial basement membrane retains many of the characteristics of the primitive fœtal type of epithelium. The cells are cubical in outline, the cytoplasm is loaded with basophilic granules, the nuclei are hyperchromatic and constantly dividing (Fig. 3); the entire layer is usually a single, occasionally a double row in thickness, and, as I have said, its similarity to the primitive type of epithelium is very striking. Overlying this arrangement and derived from it we find a distinctive and highly interesting distribution. These are the cells of the prickle group; they are larger than their progenitors, in shape they are somewhat fusiform, the nuclei are large and active, with distinct nucleoli, but the real distinction of the cell is the acquisition of prickles. These interesting and no doubt

important structures pass like stays or bridges across the intercellular spaces to be continuous with the cytoplasm of opposing surfaces. It is significant that in virtue of the prickles the intercellular spaces are wider in this second layer than in any other portion of the epithelial arrangement.

What purpose or purposes do the prickles fulfil? Probably two. To some extent they hold the cell in position, while protecting it from undue pressure by the surrounding

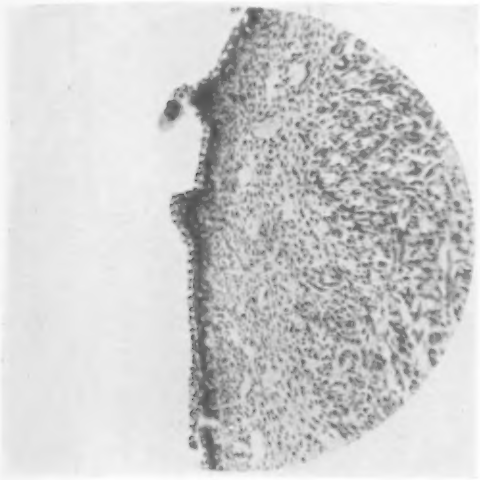
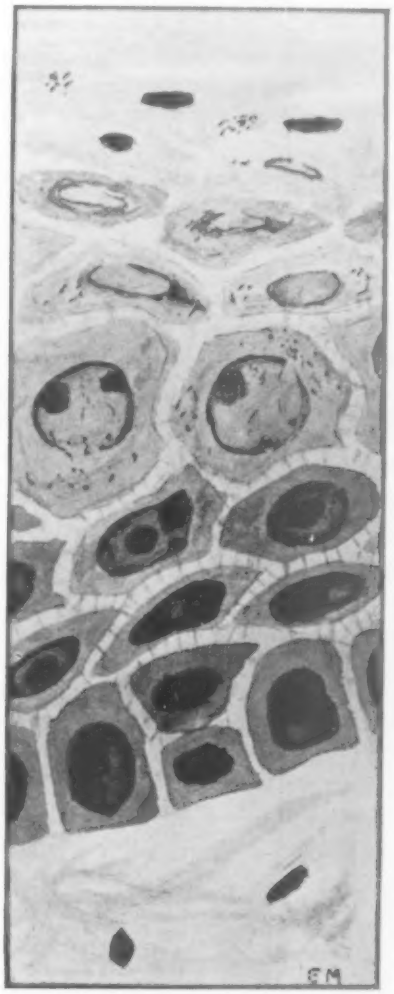


FIG. 1.



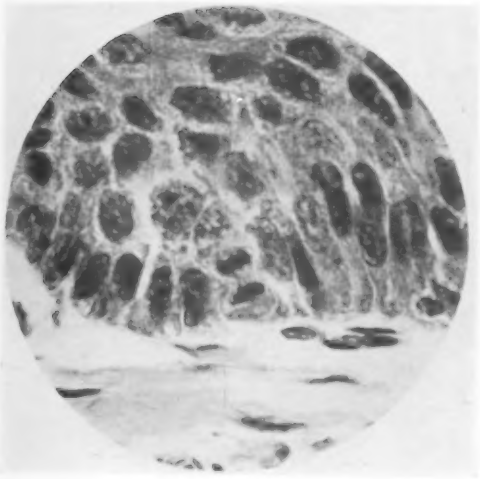


FIG. 3.

FIG. 2.

FIG. 1.—Thirty-five-millimetres Embyro. Section of dorsum of tongue showing primitive epithelium.
FIG. 2.—Diagram of cell layers in normal squamous epithelium.
FIG. 3.—Photomicrograph of normal epithelium showing mitosis of cells of basal layers.

cells, but a function of greater importance is the part which they play in maintaining a sufficiency of intercellular space in order that lymph may circulate. It would seem that, in order to maintain health and nutrition, each cell of the prickle layer shall be maintained in what is virtually a lymph bath, and it is in virtue of the prickle that this essential is achieved.

Overlying the prickle layer there is a cell group showing sufficient distinction and peculiarity to justify its recognition in a special class. Though derived from the prickle

layer, these cells possess individual characteristics. The prickle has disappeared, the intercellular spaces have accordingly vanished, and, in virtue of pressure influence, the cells have acquired a flattened and elongated outline. There is increased permeability of the cell membrane, the nuclei have degenerated, and now and then the process of nuclear rupture with escape of the chromatin may be witnessed. The phase of degeneration is further evidenced by the appearance in the cytoplasm of keratin or eleidin granules.

What is the explanation of the change? That it is degenerative in its issue is clear, but what is the feature which precipitates the alteration? It has been suggested to me by Mr. Eric Mekie, and I think he is correct, that the deciding influence is a cutting off of the lymph flow, the result, if you care to put it so, of the disappearance of the prickles, for as the intercellular space lessens, the lymph circulation is correspondingly diminished, and, as the cell nutrition is entirely lymph-maintained, an impoverishment of nutrition means cell degeneration. In the superficial or surface layers the degeneration is complete—the nucleus as such has disappeared, the chromatin is dissipated, keratin deposit (the stigma of degeneration) is abundant, and it is as dead cells that the individual elements of the superficial layer are finally dispersed.

Such are the arrangements of healthy buccal epithelium, and certain features of that arrangement must, I think, impress us, such as the evolution of the various cell elements from a common progenitor, the part which the lymph plays in maintaining the healthful nutrition of the cell, and the natural degenerative sequelæ which follow when the lymph nutrition is disturbed.

Accepting this as the general scheme upon which buccal epithelium is planned and arranged, we ask ourselves: "Is the scheme universal, or are there modifications or adaptations in different parts?" The question is of more than simple inquisitive interest, for it may be that the answer will affect our conception of the distribution and possibly of the etiology of disease. My point is this. It has been our experience that, where carcinoma of the mouth is concerned, there are sites of election, areas in which a preponderance of disease is evident, and I am curious to know whether in these special localities there are structural peculiarities which might in some measure explain an undue liability to disease. An analysis of the figures which have come under our notice indicates that the sites (Fig. 4A and B) within the mouth most frequently affected by malignant disease are:

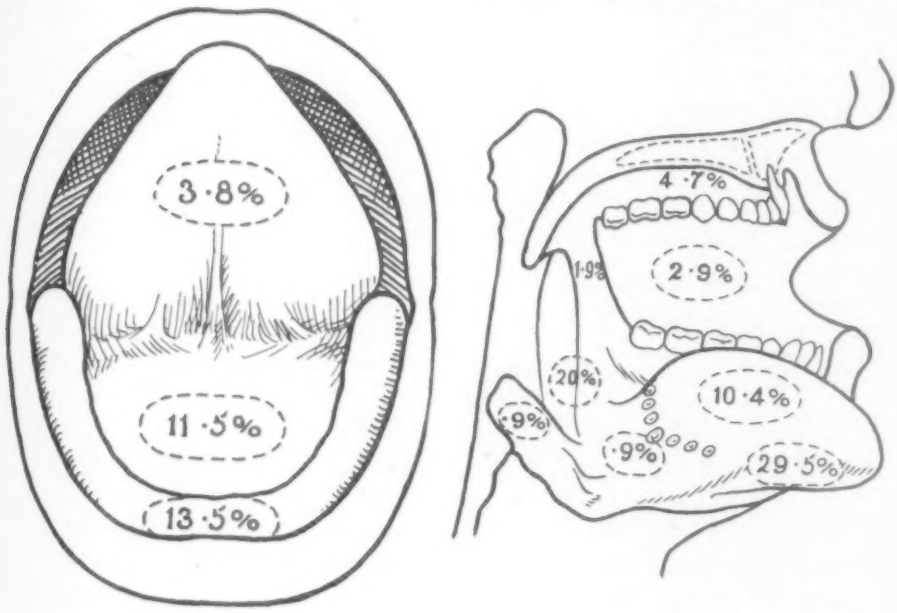
(a) The anterior two-thirds of the tongue (43 per cent.)
(b) The palato-glossal sulcus (20 per cent.)
(c) The gingivo-glossal sulcus (11 per cent.)
(d) The mouth floor (10 per cent.)

The remaining 16 per cent. appears to show no constancy of site occurrence. It seems reasonable to investigate the histological characteristics of these regions, and I propose to present a summary of our conclusions.

The Anterior Two-thirds of the Tongue.—These areas show no outstanding variation of structure. The picture is that which I have already described as being characteristic of buccal epithelium in general. It is true that at the edge of the tongue (Fig. 5), a site showing a high percentage of morbidity—68 per cent.—we find a variation in so far as the thick epithelium of the dorsum merges at this point into an epithelium which is thinner and more

"papillated" in arrangement, but this is a variation which scarcely justifies individual recognition, and we cannot say that there is any structural peculiarity in this region which might predispose the part to morbidity.

The real interest, so far as the tongue is concerned, is to decide whether there is any structural explanation of the apparent immunity to disease which is enjoyed by the posterior third in contrast to the anterior two-thirds. I anticipate that any claim to immunity may be questioned, but, so far as we have been able to discover, primary disease of the posterior third of the tongue is a rare event. I have used the term "primary" because I wish to make it clear that I do not include examples of disease which extend into the posterior third of the tongue from such surrounding parts as the palato-



A B

FIG. 4 A and B.—Site incidence of malignant disease of the buccal cavity.

glossal region, the valleculæ and the epiglottis. Observing this distinction, in forty-seven cases of primary tongue carcinoma in one instance only did the disease originate in the posterior third. The actual distribution of disease in the forty-seven cases may be of interest, and therefore I give it.

In thirty-two instances (68 per cent.) the disease appeared at the tongue edge. In fourteen instances (29 per cent.) it developed in relation to the dorsum. In one instance only was the posterior third affected. Such a relative degree of immunity must have an explanation. I do not say that structural peculiarities afford that explanation, but it is significant that the posterior third (Fig. 6) has certain distinctive points as compared with the anterior two-thirds, and they are as follow:

(1) The sub-epithelial area contains a proportion of lymphoid tissue.
(2) The epithelial layer is relatively thin.

(3) Keratinization is imperfect and there is no definite keratinized surface layer.

(4) The prickle-cell layer is deficient or even entirely absent.

(5) The deep granular layer is well developed.

(6) There are numerous racemose glands in the sub-epithelial space.

The question whether or not the relative freedom from morbidity is due to one or more of these structural distinctions cannot be answered with any measure of assurance, but there are certain possibilities which suggest themselves. I believe, for example, that the existence of lymphoid tissue in this area affords a measure of resistance to a malignant epithelial change. We have a great deal to learn about the part which the lymphocytes play in resisting malignant epithelial invasion. It is certain that a lymphocyte-cell barrier surrounds the early infiltration of a malignant epithelial cell. Another feature which may lessen the tendency to morbidity in this situation is the relative absence of cell differentiation, the tendency being for the cells to remain as the primary cubical and granular type rather than to acquire the differentiating features of prickle and keratin. This, however, is mere hypothesis, and we have no definite knowledge of the tissue factors as they affect morbidity.

The Palato-glossal Area.—I have alluded to the fact that 20 per cent. of buccal carcinomata originate in the palato-glossal area. There is reason to believe that this high proportion is to some extent explained by peculiarities of structure which may be predisposing to disease. If we examine that portion of the tongue edge (Fig. 7) which comes into contact with the anterior pillar of the fauces, we find certain indistinct vertical ridges of epithelium (the papilla foliata). They are the remnants of a structure which reaches its fullest degree of development in rodents and the lower primates, a multiple crypt-like arrangement the walls of which are provided with numerous taste buds (Fig. 8), so that the flavor of food held in the hollow of the cheek is fully appreciated. In man the structure is an atavism—the taste buds have disappeared, but the crypts remain, so that large numbers of epithelial cells without any definite or specified function are grouped within these confines. The fact that collections of these cells may be almost entirely cut off from communication with the surface probably adds to the potentiality of danger. It is believed that cells of this type and under such conditions are frequent sources of malignant change (Fig. 9) and, if we support this view, we may well agree that the relatively large percentage of malignant morbidity in this area owes part of its incidence to predisposing structural peculiarities.

The Floor of the Mouth.—In this region of the mouth 10 per cent. of carcinomata occur, and on a closer analysis it is evident that the majority of these are localized around the openings of the salivary ducts (Fig. 10). Such localities bespeak junctional epithelium, and it is possible that in this structural peculiarity we find at least one etiological factor.

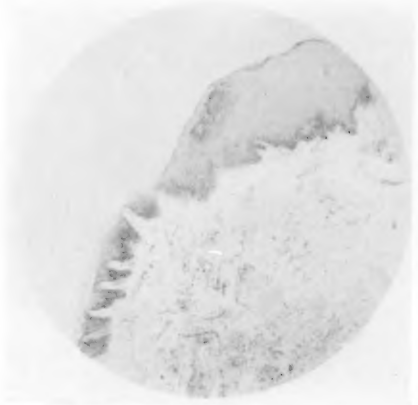


FIG. 5.—Edge of tongue.

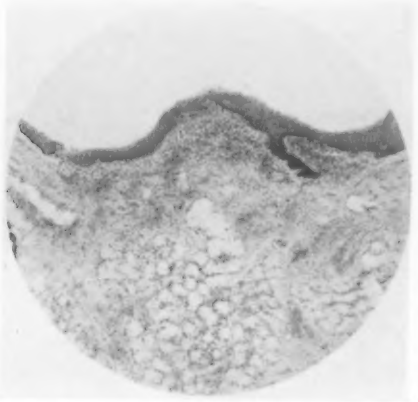


FIG. 6.—Dorsum of tongue in posterior third.

FIG. 7.—Rabbit's tongue.

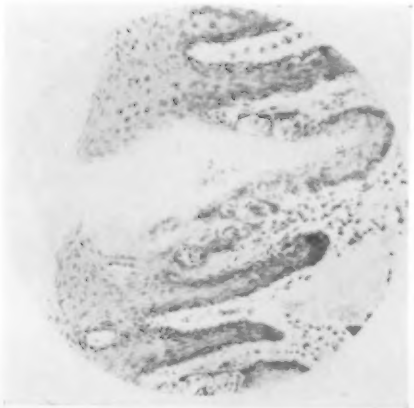


FIG. 8.—Rabbit's tongue. Folia lingulæ showing taste buds.

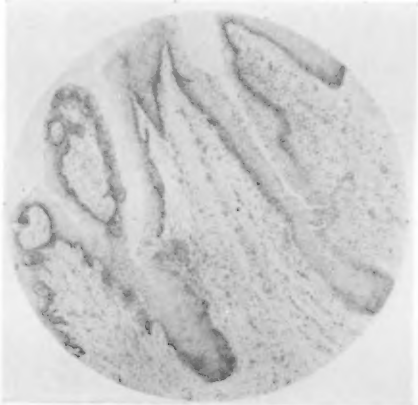


FIG. 9.—Folia lingulæ.

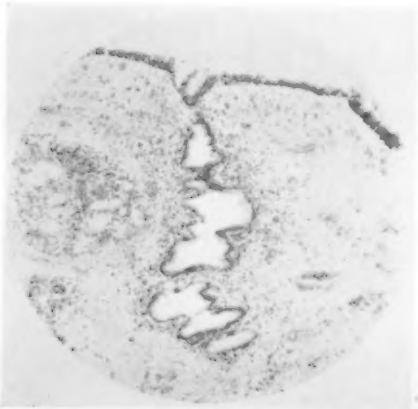


FIG. 10.—Duct of mucous gland in floor of mouth.

The Gingivo-glossal Sulcus.—Here there is no evident factor of special tissue arrangement. The epithelial arrangements are uniform and complete, and it is evident that the etiological factor which individually affects this region is something apart from any structural peculiarity.

I would sum up this whole matter of epithelial arrangements by saying that in two situations—the palato-glossal sulcus and the floor of the mouth—we find conditions of cell distribution such as may constitute predilection to neoplasm, while in the posterior third of the tongue the tissue arrangements

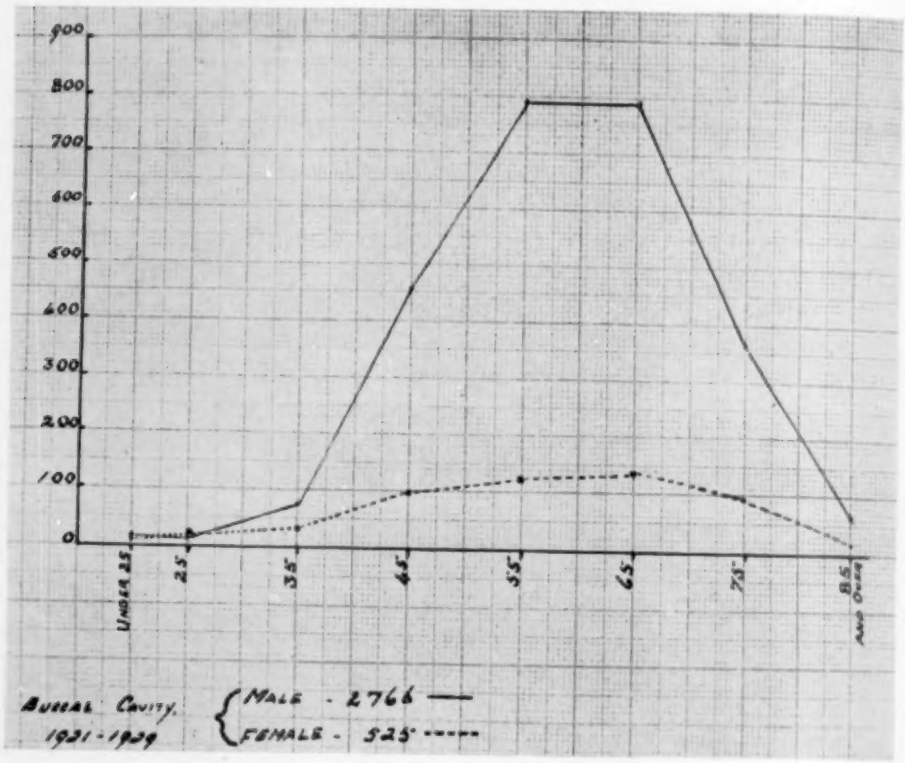


FIG. 11.—Age incidence of buccal carcinoma. (Scotland.)

are such as may confer some degree of unusual resistance of the parts to such a change.

If such structural peculiarities as I have outlined play a part in the site incidence of mouth tumors, there are other influences which act as the stimulus in the production of the erratic cell growth which constitutes malignancy. Let me review such influences as may seem to play a part in the so highly debatable problem of etiology.

Age is the first consideration, and it has this importance that as the years advance the liability to the disease appears to increase, so that the maximum incidence occurs in the decade between seventy-five and eighty-five years (Fig. 11). It is obvious that the proportion of individuals who reach such an age

is relatively small, and in any estimate of the proportional occurrence of the disease this fact must be taken into account, but, when various corrections are made, it is evident that with increase of age there is increased liability to the disease. The explanation of age influence is debatable (Fig. 12), but in all likelihood it may be taken as meaning that cell instability increases as age advances, so that a stimulus which in younger tissue would pass unnoticed now induces the change that results in malignancy.

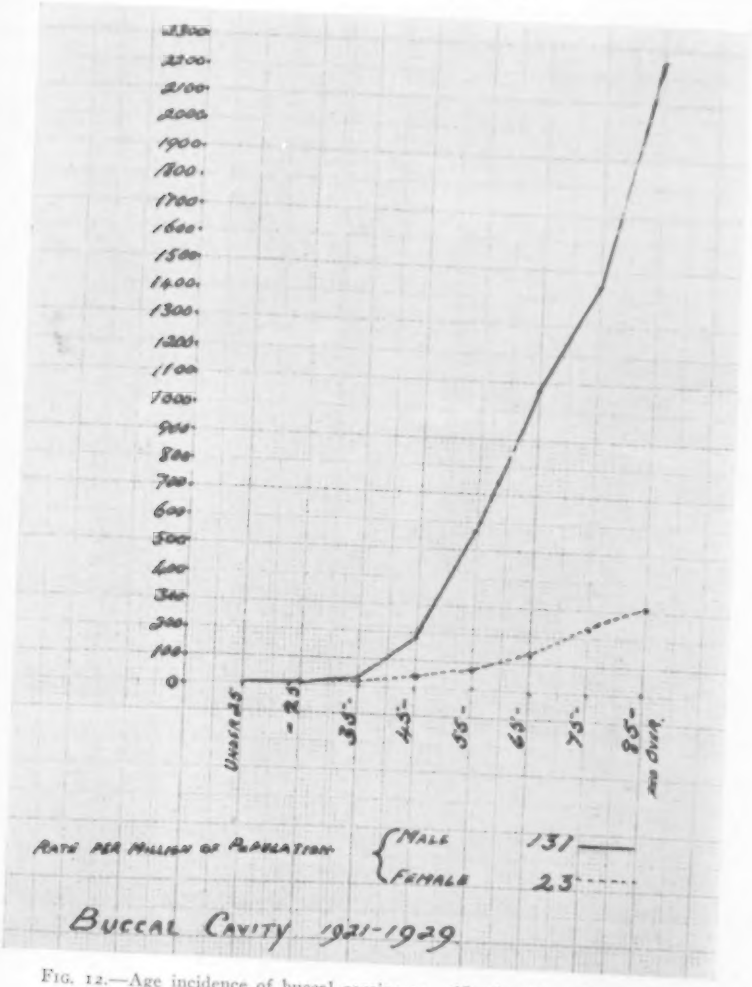


FIG. 12.—Age incidence of buccal carcinoma. (Scotland.) (Corrected.)

Sex.—It is common knowledge that mouth carcinoma is more often met with in males than in females in a proportion of eight to one, and it is agreed that the higher sex incidence of the male is explained by the greater degree of injury which he inflicts upon his buccal mucous membrane by such irritants as spirits and tobacco. Confirmation of this would seem to be supplied by statistics from Southern India and Ceylon, where the incidence of buccal

carcinoma is greater in females owing to the fact that they indulge in the habit of chewing betel, a combination of tobacco, areca nut, and slaked lime. There is the further factor that the average female is probably more careful about her teeth and mouth hygiene, and in so much she preserves herself from the irritation and stimulus of infection.

Heredity as an influence is a matter which I shall not discuss because I have not sufficient knowledge to assess its importance, but I would like to record an experience which suggests that an indirect heredity—the transmission of an enhanced liability to the disease—may exist. Three brothers, A, B, and C, living under different conditions, developed buccal carcinoma, and all three cases appeared within a period of two years. Their father, an uncle, and an aunt had succumbed from epithelial carcinoma. The coincidence is suggestive, but its exact significance must for the present remain in doubt.

Syphilis has long been recognized as being in some way intimately associated with the development of mouth carcinoma. Literature contains abundant references on the question, and Poirier once expressed his views in the somewhat cryptic phrase that "Cancer of the tongue is a disease of syphilitic smokers." In a recent analysis of seventy cases of mouth carcinoma we have found that 14.7 per cent. afforded evidence of a former syphilitic infection. This is a smaller proportion than is usually recorded, but the real interest of the analysis lies in what might be regarded as a secondary point. If we estimate the proportion of syphilis in relation to the site at which the carcinoma occurs we find that in tongue carcinoma the syphilitic proportion is 42.3 per cent., and where the malignant disease affects the dorsum of the tongue the syphilitic incidence rises to 78.3 per cent. What is the explanation? It may be that the vascular changes of a syphilitic infection are more fully exercised in the tongue dorsum than in other situations, but there is evidence to show that the association is certainly related to the condition of leucoplakia. Dorsal tongue leucoplakia is one of the most frequent associations of former syphilis, and in 90 per cent. of cases, dorsal tongue carcinomata are preceded by leucoplakia. The close relationship between dorsal tongue carcinoma and syphilis thus seems to be established.

Tobacco as an etiological influence is difficult to estimate. What would seem to be a convincing statement of its importance is found in Turner's report to the British Colonial Office in 1905 on the incidence of buccal carcinoma among the Spaniards of Gibraltar. In our series (105 cases) we have to record that in eighty-eight male cases sixty-five were heavy pipe smokers, and of the remaining thirteen there was no individual who was a rigid non-smoker. Of tobacco it may be said that the drug (if I may call it so) in itself does not produce the disease, but in conjunction with one or more irritants of a general or local type, it may be a factor in inducing the cell changes which result in malignancy.

Alcohol, and particularly raw spirit, is probably rightly regarded as an important factor in the production of the disease. Figures furnished by the Registrar-General of Scotland indicate what I might term the geographical distribution of mouth carcinoma. In two countries the incidence figure is unduly high, and it is significant that these are areas in which the drinking of raw spirit is prevalent. It is probable that the influence of alcohol on tissue change is twofold; in part it is a surface irritant, in part it acts as a circulatory toxin, at first stimulating tissue growth, later inducing a degenerative change on the tissue it has previously stimulated, and it is not surprising that, when imbibed in a concentrated form, it plays some part in the production of carcinoma. In the series which forms the basis of this paper (105 cases), twenty were admittedly heavy spirit drinkers, but it is obvious how difficult it is to obtain accurate information on such details, and the proportion may well have been higher.

Mouth infection is in our view the most constant and prevailing associated influence, and we have no doubt that it plays a highly significant part in the production of the malignant error. An analysis shows that at least 50 per cent. of the cases were infected with pyorrhœa alveolaris prior to the development of the cancer, and from what we have seen we are satisfied that this influence is one of the most significant in the etiological picture, that it is the most constant and common factor, and that its influence is increased when it is combined with other irritant factors such as alcohol, tobacco, syphilis, or direct local irritation. It is probable that, as in the case of alcohol, the effects of infection are exercised locally and generally.

Direct Local Irritants.—It is an accepted truism that local irritants in any shape or form influence the production of carcinoma and in the sensitive and almost unstable epithelium of the mouth the principle has peculiar importance. The series of cases under review has many examples illustrative of this. The sharp-edged tooth and the ill-fitting denture were recorded in several instances; in two cases the disease began in the mucous membrane of the alveolus contiguous with a tooth-filling which, occupying the lowest part of the tooth, came into contact with the epithelium. It is probably more than a coincidence that in both cases the filling was found to contain an element which I understand is unusual in dental therapeutics—antimony.

In conjunction with this it is well to record the occurrence of a carcinoma of the tongue in an antimony worker aged sixty-three years (C835). He acted as an antimony "feeder" for seventeen years (1898–1915). In the later years of his service he developed an eczematous condition of the forearm, a pronounced hyperplasia of the palmar skin and a buccal leucoplakia. It was the development of these errors which induced him to abandon his work. He came under our care in 1925, suffering from a carcinoma of the tongue. It is necessary to add, for it may indicate the influence of superimposed irritants, that he was a heavy smoker, and showed a strongly positive Wassermann reaction.

In two instances tar irritants may have been the responsible factors. One case worked in the fumes of tar paper (E919, aged sixty-three years). He developed a carcinoma of the lower lip, and eighteen months later an epithelioma on the buccal surface of the cheek on the opposite side. The other was a roadman tar sprayer (A840, aged sixty-three years), who developed a carcinoma on the buccal surface of the lower lip.

I must add that where carcinoma of the mouth is concerned we find evidence of a tendency which, though no doubt manifest in malignant disease elsewhere, is particularly noticeable in carcinoma of the buccal epithelium. I allude to the liability which there is in certain individuals to what may be termed epithelial instability, the tendency for a malignant change corrected at one point to reappear at subsequent dates in other situations within the mouth. There were five examples of this tendency in our series of 105 cases, and the facts regarding the occurrence may be summarized as follows:

A. suffered fourteen years ago from an epithelioma of the lower lip—he has recently been under treatment for a cancer of the right palato-glossal fold (B283); B. was affected with a rodent ulcer of the left nostril twelve years ago—there is now a cancer of the left palato-glossal fold (A953); C. developed an epithelioma of the lower lip fifteen years ago—six months ago cancer appeared in the left edge of the tongue (A810); D. developed an epithelioma of the left side of the tongue in 1916—eight years later a similar tumor appeared on the right side of the tongue, which was successfully treated, but two years later there was a further development (B568); E., affected with an epithelioma of the left lower lip, developed the same condition in the buccal surface of the right cheek seven months later. It is significant that in four out of the five cases the time intervals between the occurrence of disease were fourteen, fifteen, and eight years respectively. It is difficult to assess the importance which should be attached to this observation. Is it an indication of an inherent instability of buccal epithelium? Is it a response to a persisting etiological influence or is it merely a coincidence? Its significance in the life history of the individual is apparent.

These are some of the factors which a study of the etiology would appear to bring out. There are certain localities within the mouth which in virtue of structural peculiarities appear to have a predisposition to epithelial instability, and it is possibly this association which explains the high incidence of the disease in these situations. There are factors which act as direct local irritants of the surface epithelium, such as the mechanical influence of the ill-fitting denture, the chemical stimulus of alcohol, of tobacco, and of dental sepsis. There are factors of a more general influence, syphilis and alcohol, which, brought to the tissues through the medium of the blood and the lymph-stream, induce a tissue change at first stimulant, later degenerative, which probably plays an important part in inducing the neoplastic change. Underlying these individual and specific influences there are the more intangible

factors of inherent cell instability and the degenerative changes which appear to be natural sequelæ of advancing age. The etiological factor in an individual case may be any one of these influences, and in all likelihood a combination of influences plays a part in the majority of instances.

The Pathology of the Lesion.—When we consider malignant disease of the mouth from the pathological standpoint it is convenient to group the lesion into two classes: (*a*) Those which demonstrate a uniform type of pathology, commonly known as the *epitheliomata*, but which from cytological and morphological considerations are more accurately termed *acanthomata*; and (*b*) a group of tumors the pathology of which has features quite atypical of the changes one associates with buccal epithelium. Tumors in the second group are rare; their individual characteristics, clinical and pathological, vary with each type. There is much of interest in their several distinctions, and, if time permits, I shall allude to them later, but for the present let us visualize the sequence of events as it is pictured in the characteristic and common epithelioma or acanthoma.

There is, I think, general agreement that the cell which invades the sub-epithelial area is one of the cubical and basement cell group. That is the view expressed by Broders, Ewing, and by Mekie, and, when we consider the question, it is difficult to see how it could be otherwise. It is evident from the study of the normal epithelial arrangements that the basal cell is the one which is endowed with the capacity of mitotic division; in fact, it is possible that it is the only cell of the buccal epithelial group which is so endowed, the other cells being offspring which themselves are incapable of independent division, but which pass through a life cycle of varying adaptation of form. If this is the correct conception, and there is much to be said in favor of it, we must believe almost of necessity that the basement cell (Fig. 13) is the originating factor in the histogenesis of the epithelial tumor.

Let us trace the further evolution of the cell changes (Fig. 14). Whatever the stimulus may be which leads to the change, there is a migration of the basement cell through the sub-epithelial membrane into the sub-epithelial tissues. The advance takes place in a variety of ways—in lines of infiltration spread, in rounded club-shaped cell groups, in a uniform mass invasion. Different types of invasion may exist in the same tumor (Fig. 15), but as a rule there is a degree of uniformity in individual tumors, so much so that the type of cell invasion can often be surmised from the clinical appearance of the tumor, the fissured epithelioma indicating the narrow infiltration spread, while the nodular tumor is likely to be associated with the mass type of invasion.

Invasion having occurred, what is the further progress of events? In what may be considered characteristic circumstances the cellular changes pass on to cell-nest formation (Fig. 16), and when we investigate the process we find that the metamorphosis we are witnessing is a reproduction of the process we have already witnessed in normal epithelium. This is a remarkable finding, and there are comparatively few parallels in histopathology. As

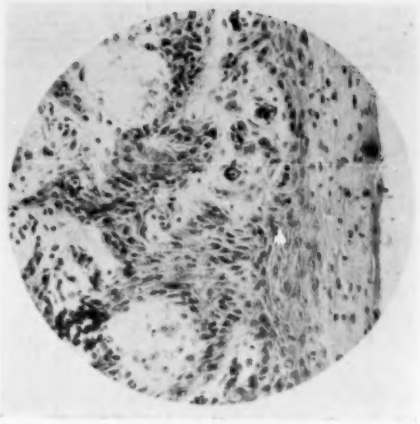


FIG. 13.—Origin of acanthomata. Down growth of basal cells.

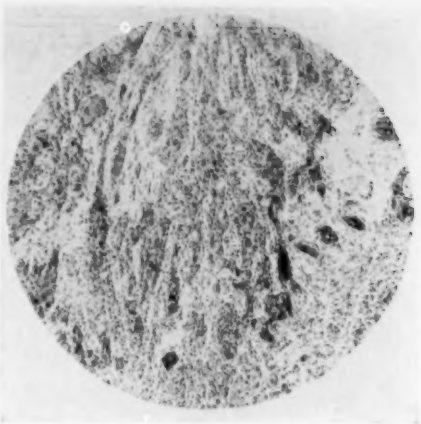


FIG. 14.—Method of down growth. Strand formation.

FIG. 15.—Method of down growth. Club formation.

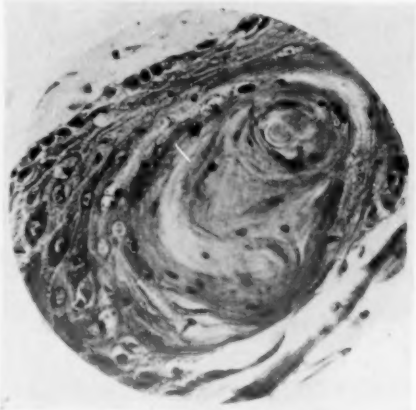


FIG. 16.—Structure of cell nest.

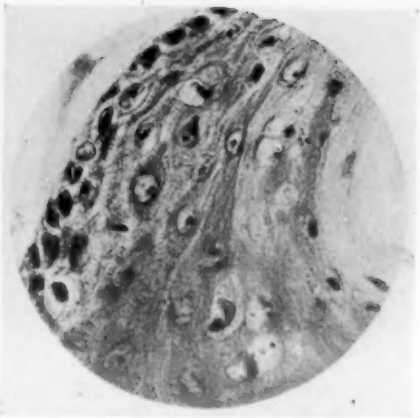


FIG. 17.—Cell layers in a cell nest.

we trace the invading cubical cells we find that they tend to arrange themselves in concentric groupings. Those at the periphery show abundant protoplasm of a granular and basophilic type, while there is abundant mitosis of the deeply staining nucleus. More centrally the cells are fusiform in outline, they are provided with prickles, and they lie tangentically to the central axis of the group. The protoplasm is swollen in appearance, and shows an eosinophilic staining reaction, while the nucleus has increased in size. Still more centrally, the nuclear membrane ruptures, its chromatin passes into a

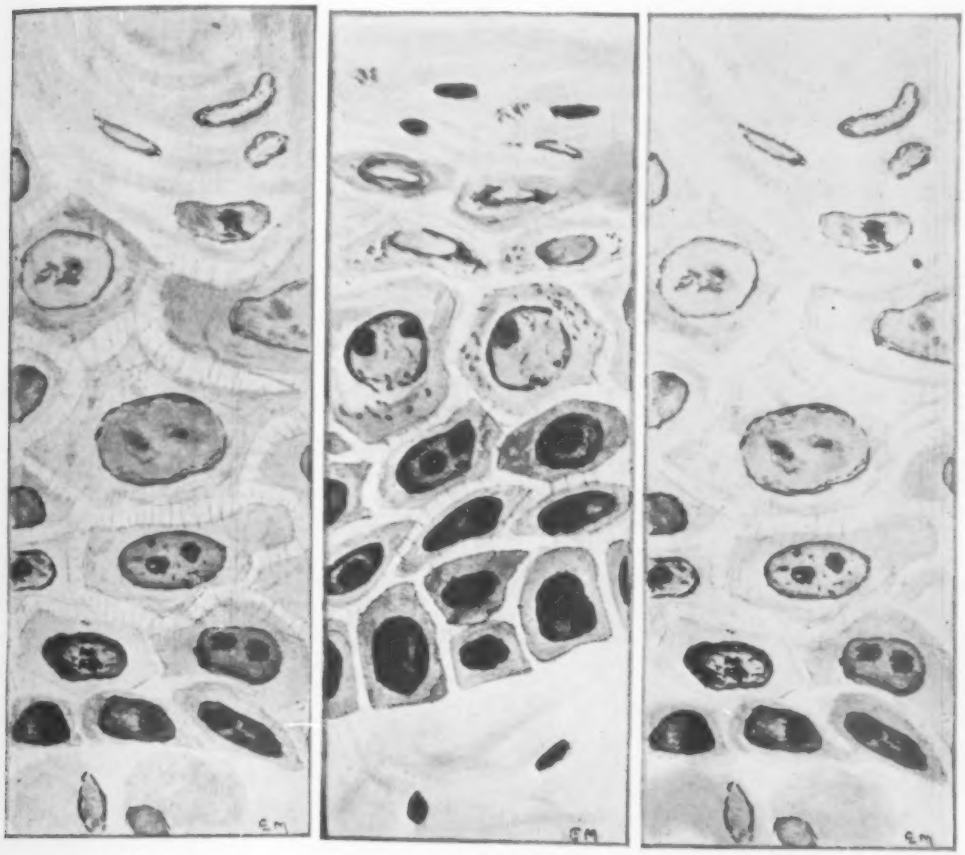


FIG. 18. FIG. 19A. FIG. 19B.

FIG. 18.—Diagram showing cell layers in acanthoma.
FIG. 19 A and B.—Comparison of cells of normal epithelium and those of cell nest.

cytoplasm which is now a homogeneous structureless mass, and it is the concentric whorl-like arrangement of this substance interspaced with fragments of nuclear membrane and chromatin débris which gives the appearance of the cell nest (Fig. 17). What we have witnessed has been a metamorphosis of the cell from cubical basement epithelium to the stage of complete keratinization, circumstances of position and of tissue tension having resulted in striking alteration in cell arrangement, but the change is a reproduction of a

natural process under altered conditions, and for that very reason assuming features of pathological significance (Fig. 18).

While these are the changes which we regard as characteristic of a malignant degeneration, typifying as they do the successive stages in the life history of the cell (Fig. 19), we must recognize that in many instances the process is not carried to such an ultimate sequel, that it may be arrested at varying stages of the process. It may be that the tumor is constituted by cells of the cubical type, and that no variation from this can be discovered; on the other hand, the evolution may extend to the stage of the large, flat, squamous cell, the prototype of the prickle cell; while in a third group (and they constitute the majority) the variation presents the complete picture of cell distinction from cubical epithelium to full keratinization. It has been suggested by Broders that the term "differentiation" is that which most fully expresses the changes which the cell may undergo.

It is appropriate at this stage to make allusion to the work of Broders on the subject of the differentiation in so far as it may affect the malignancy of the tumor and the prognosis of the individual. Broders recognizes four grades of tumor type according to the degree of differentiation of the cell. He accepts cell-nest or pearly-body formation as the standard of complete differentiation, the large, flat, squamous cell with small nuclei and early keratinization as indicating partial differentiation, while the cubical cell represents an undifferentiated state. On this basis he groups the cell incidence in the various grades as follow (Figs. 20, 21, 22 and 23):

Grade I	Differentiated, 75 per cent. Undifferentiated, 25 per cent.
Grade II	Differentiated, 50 per cent. Undifferentiated, 50 per cent.
Grade III	Differentiated, 25 per cent. Undifferentiated, 75 per cent.
Grade IV	Differentiated, 0 per cent. Undifferentiated, 100 per cent.

Such a classification or grouping has certain significance. It is of value for descriptive purposes, and the conception which it implies has a certain scientific merit, but it is as an index of the clinical state that its most significant application lies, for it would seem beyond dispute that it is in the undifferentiated type that the greatest malignant potentiality exists.

We have analyzed the tumor types in our series on the basis of Broders' classification, and the results may be indicated as follow:

Group	*Percentage*
I	48 per cent.
II III	36 per cent.
IV	16 per cent.

The Influences Which Control Differentiation.—It is reasonable that we should ask ourselves: What is the factor which controls the variation in

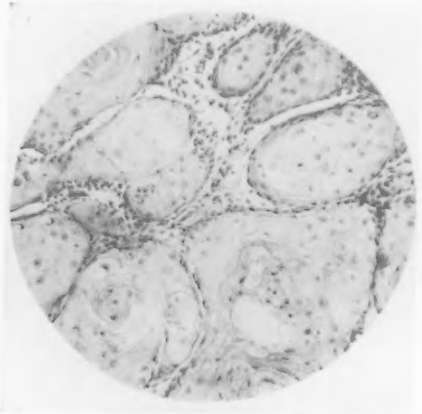


FIG. 20.—Squamous epithelioma. (Broders Type I.)

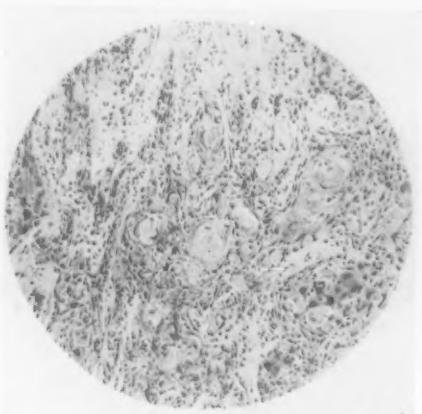


FIG. 21.—Squamous epithelioma. (Broders Type II.)

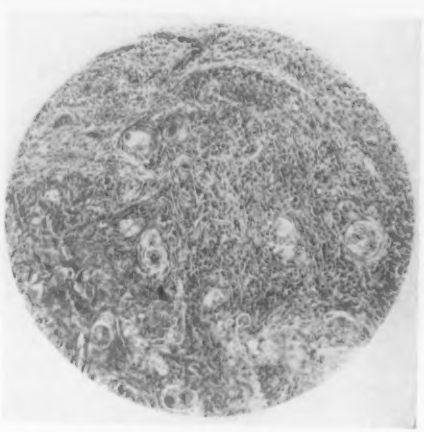


FIG. 22.—Squamous epithelioma. (Broders Type III.)

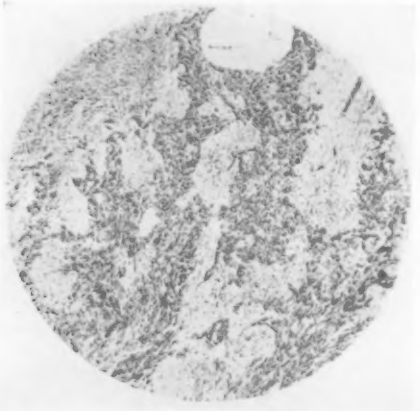


FIG. 23.—Squamous epithelioma. (Broders Type IV.)

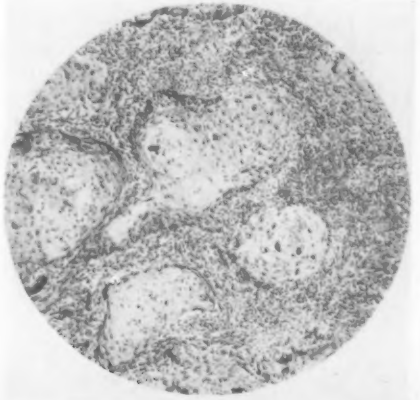


FIG. 25.—Intense lymphocytic reaction to tumor.

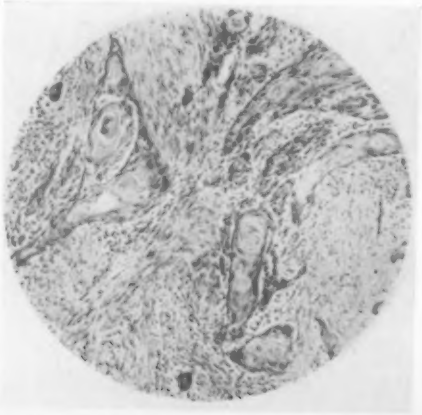


FIG. 26.—Fibrous reaction to tumor.

differentiation in these tumors? (Fig. 24.) It may be that it is a matter of inherent variability in the cell, an influence which is too indefinite and intangible to permit of definition, but on the other hand there are indications that the explanation is a demonstrable one. It will be recalled that the variation in normal epithelium may depend upon nutritive factors; the cubical basement cell produces the large prickle one, a cell which is bathed in lymph, and which maintains its vitality by a process of absorption from the lymph (Fig. 25); as we approach a more superficial level the lymph circulation is either lessened, or its efficiency curtailed, with the result that degenerative changes appear and keratinization ensues. (Mekie.) If this be the normal process of events, it is not unreasonable to argue that the variations encountered in tumor formation have a similar explanation (Fig. 26). If nutrition is maintained when the basement-cell invasion occurs, the likelihood is that the characters of a cubical-celled tumor will be demonstrated; if, on the other hand, nutrition is imperfect, the various processes of differentiation or of degeneration appear, until the full keratinization of cell-nest formation is

	Broder's Types 1 and 2.		Broder's Types 3 and 4.	
	Basal cell reg.	Basal cell irreg.	Basal cell reg.	Basal cell irreg.
Lymphocytic reaction marked.	6 (12.7%)	6 (12.7%)	0 (0%)	4 (8.5%)
Lymphocytic reaction not marked or absent.	10 (21.3%)	3 (6.3%)	4 (8.5%)	14 (29.9%)

FIG. 24.—Factors influencing type of neoplasm.

manifest. In other words, if this argument is correct, the variation of tumor types is controlled by the factor of nutrition (Figs. 27A and B).

I recognize that this is by no means the end of the story, that there are factors which must underlie nutrition—body defensive mechanisms, such as lymphocyte barriers and influences of tissue tension—but these possibilities open up fields beyond the scope of our present discussion.

Atypical Tumors.—As I have already indicated, there are certain tumors arising from buccal epithelium which cannot be included under the acanthomata group, and their variations are so great that it is impossible to include them under any single collective heading. I propose to do no more than mention the individual types which we have encountered.

(A) *Spindle-celled Epithelioma* (Fig. 28).—In this instance a warty tumor the size of a marble developed on the margin of the tongue. Microscopically, the tumor appeared to originate from the basement cells of the epithelium, but, instead of assuming the variations of the acanthoma group, the cells presented a most curious fusiform appearance, so much so that the pathologist who examined them raised the possibility of the tumor being a fibrosarcoma.

(B) *Mucoid Epithelioma.*—We have used this descriptive term because of the peculiar degree of mucoid degeneration in the tumor stroma. The clinical characters

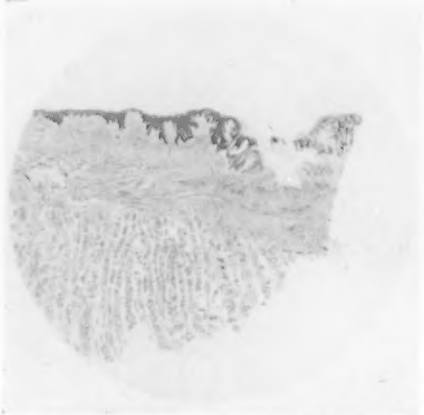


FIG. 27A.—Macroscopical types Ulcerative.

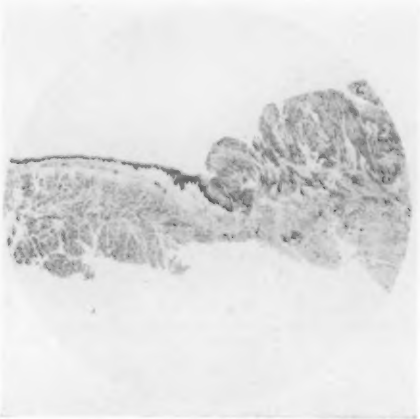


FIG. 27B.—Papilliferous.

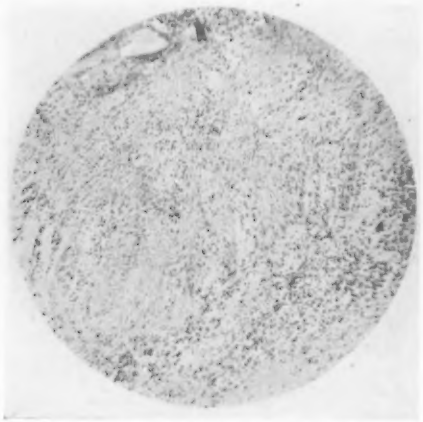


FIG. 28.—Spindle-cell epithelioma.

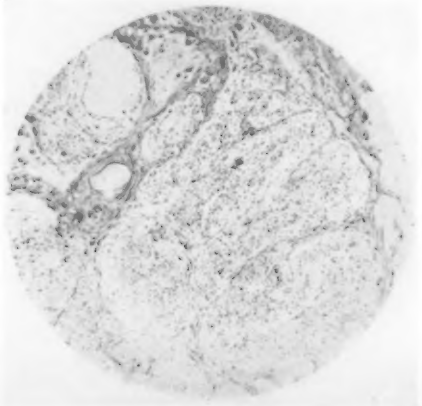


FIG. 29.—Mucoid epithelioma.

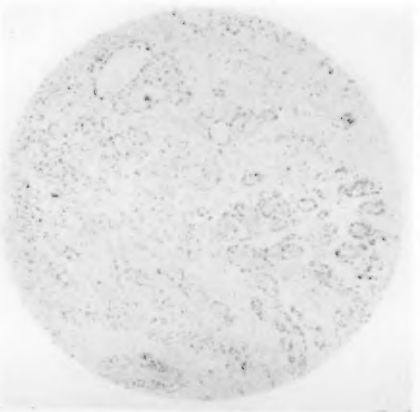


FIG. 30.—Alveolar epithelioma of floor of mouth.

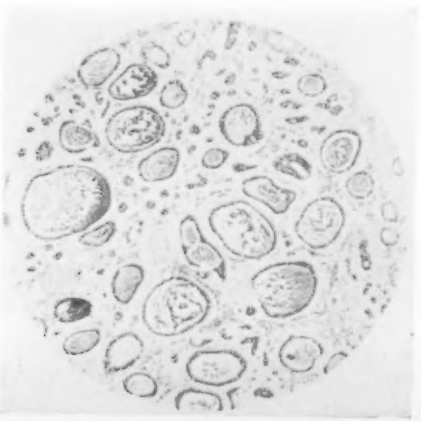


FIG. 31.—Admantinoma of alveolar margin.

were those of a small nodule at the tip of the tongue showing surface ulceration (Fig. 29). The tumor was composed of cells showing the characters of basal cells, the invasion was by means of migration into the sub-epithelial area, but the distinctive feature was the remarkable degree of mucoid degeneration in the surrounding stroma.

(C) *Alveolar Epithelioma.*—In this instance the clinical features were those of a non-ulcerated tumor of the gingio-lingual sulcus immediately lateral to the frenum (Fig. 30). The histopathology was that of a basal-celled epithelioma in which the cells assumed a peculiar acinar-like arrangement. The structure was not unlike the appearance of salivary tissue in an early stage of development, and the suggestion is that the tumor may have originated from a portion of epithelium designed to form salivary or submucous gland tissue.

(D) *Adamantino-epithelioma.*—A tumor originating from the alveolar margin (Fig. 31) of the lower jaw in contiguity with a tooth was found to present the appearance of solid masses of cells showing in the centre a reticular change similar to that in the nucleus of a developing tooth, and it is suggested that in this case a basal-celled tumor originated in that portion of the epithelium which was concerned with the development of the tooth germ.

(E) *Mixed Tumor of Salivary Gland Origin.*—A slowly growing tumor of six years' duration originating from the right tonsil and presenting a smooth non-ulcerating surface was found on microscopical examination to show characters of a complex type similar to those of a mixed tumor of salivary gland origin (Fig. 32). Squamous epithelium, acinar epithelium, and myxomatous tissue were present.

(F) *Endothelioma.*—A small ulcerating tumor of the hard palate (Fig. 33) was revealed as an endothelioma.

(G) *Melanoma.*—In two instances an ulcerating and pigmented tumor of the hard palate showed the typical appearance of a melanoma (Fig. 34).

(H) *Lympho-epithelioma.*—A bulky, rapidly growing tumor of the right tonsil (Fig. 35) was found to consist of basal cells combined with numbers of large cells of the lymphocyte type. The microscopical characters of the tumor were similar to those described by Regaud under the title of lympho-epithelioma.

(I) *Tumors of the Transitional Cell Type.*—In three instances tumors originating apparently from buccal epithelium assumed the characters of the transitional type (Fig. 36) as encountered in tumors of the urinary tract, the cells being arranged along strands of vascular connective tissue.

I have alluded to these various atypical tumors in order to remind ourselves that, while the acanthoma group is that which is most truly representative of buccal epithelium pathology, a variety of atypical types may present themselves.

The Methods of Spread.—The original tumor formation extends by certain recognized modes and channels—by local invasion, particularly along fascial planes, by lymphatic spread (Fig. 37), by blood spread, and by a method which is really a variety of lymphatic spread, infiltration along the perineural spaces. The method of local invasion is that common to carcinomata in any situation; the lymphatic spread is usually in the perivascular and perineural lymphatics. In the immediate proximity of the tumor the mode of spread is by permeation, but this method appears to cease in the environs of the tumor, and thereafter it appears to be by a vehicular or embolic spread (Fig. 38). The blood dissemination of an epitheliomatous tumor is recognized as an unusual event. In three instances we have been

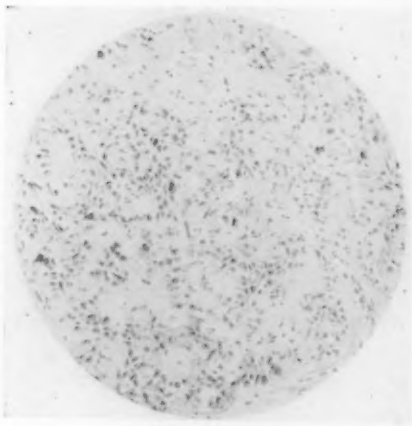


FIG. 32.—Mixed tumor of palato-glossal area.

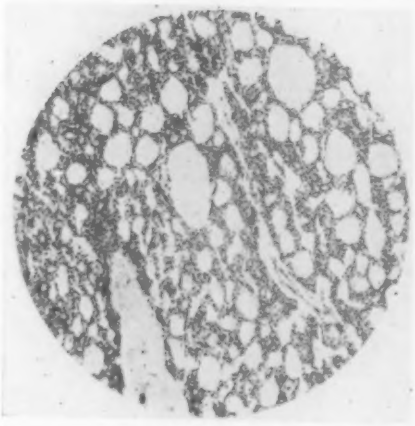


FIG. 33.—Endothelioma of palate.

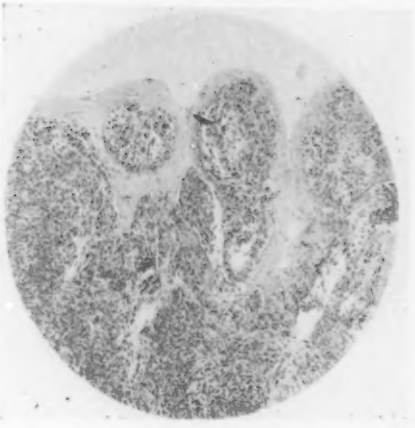


FIG. 34.—Melanoma of palate.

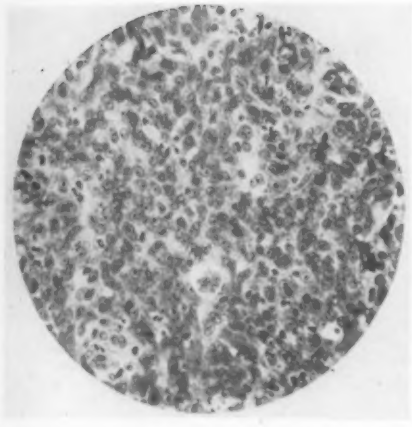


FIG. 35.—Lympho-epithelioma of tonsil.

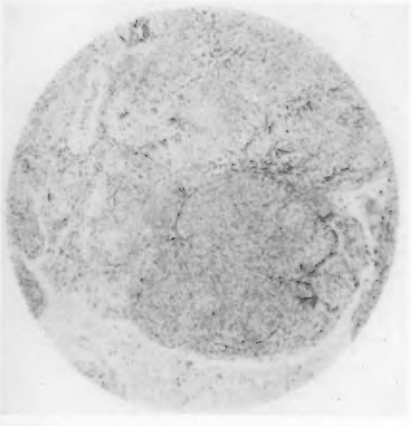


FIG. 36.—Transitional type of epitheliomata.

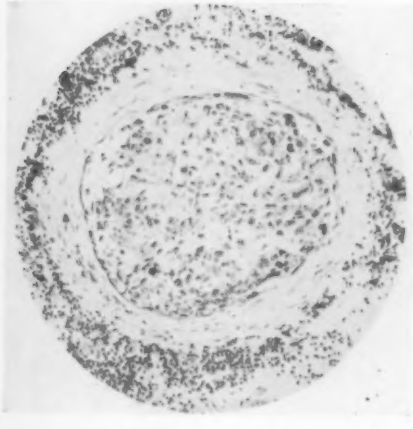


FIG. 37.—Lymphatic spread of tumor.

able to demonstrate invasion of a blood-vessel by a malignant infiltration, so that a carcinomatous plug occupied the vessel lumen (Fig. 39). In each instance the original tumor was of a peculiarly vascular type. (Group IV.) Blood dissemination, however, is not a serious risk, because it would seem that the epithelial malignant cell is unable to exist for any length of time in the blood-stream (Fig. 40). It is this fact which explains the rarity of visceral metastasis as a sequel to buccal carcinoma. As regards perineural spread, referred nerve pain is one of the most distressing features of an established buccal carcinoma. It may be that the explanation is afforded by this phase of the pathology, for the observer is at once impressed by the frequency with which a perineural spread is observed (Fig. 41). No doubt the perineural lymphatics are the actual channels of the conveyance, but the contact with the nerve elements is very close and in several instances the nerve bundles have been infiltrated (Fig. 42). It is at once evident that such a condition must be associated with nerve pain, but whether it can be accepted as a constant explanatory factor is doubtful (Fig. 43).

The Problem of Treatment.—However deep may be our interest in questions of etiology and pathology, we recognize that as practical surgeons it is the problem of treatment which most intimately concerns us. The subject is a difficult and in some respects a distressing one, for we cannot be blind to the fact that, except in certain chosen and early cases, the results obtained give us cause for anxiety. We have analyzed our records in respect of treatment, as they are presented over a period of ten years, and I think some interest attaches to them, as they concern a variety of methods and afford therefore a basis for comparison.

The general term "surgical treatment" may cover any of the well-accepted methods.

(1) Excision of the tumor by scalpel or diathermy, together with a radical dissection of the related lymphatic field.

(2) Radium or X-ray treatment of the local area, combined with radical dissection of the lymphatic field.

(3) Radium or X-ray treatment of both the local and the lymphatic areas.

We have had an opportunity in a modest way of evaluating the results of certain of these procedures, and, though I recognize that our figures are too few to be of real value from a statistical point of view, I propose to present them to you.

(1) *The Operation of Radical Excision.*—Until the advent of radium therapy this, of course, was the method universally employed. The procedure was and still is in certain cases to remove the affected area by a wide excision, using the scalpel in the majority of cases, diathermy in a minority. A radical dissection of the related gland groups is an obvious corollary to the central operation, and it is apparent that this stage of the procedure may

FIG. 41.—Blood spread of carcinoma. Malignant cells free in blood-stream.

FIG. 42.—Commencing infiltration of nerve by malignant cells.

FIG. 43.—Neural invasion.

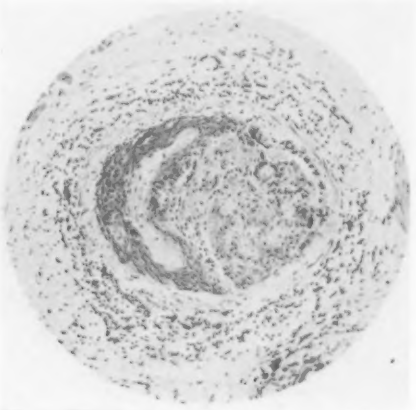


FIG. 38.—Lymphatic spread of tumor, with commencing cell-nest formation.

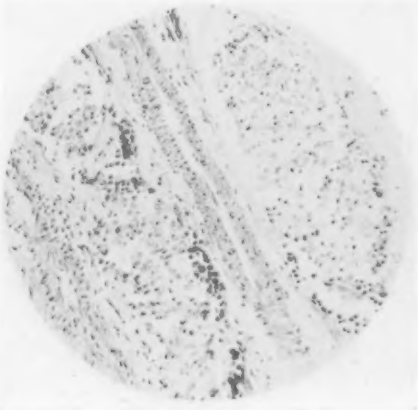


FIG. 39.—Invasion of perivascular lymphatics.

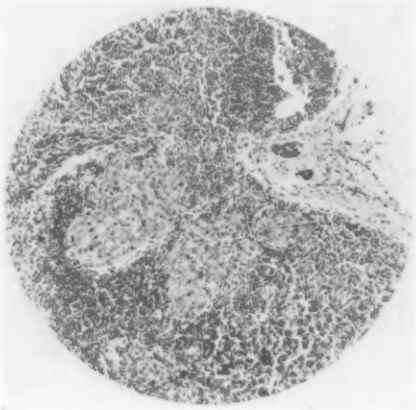


FIG. 40.—Malignant embolus arrested in capsular lymphatic with endothelial reaction.

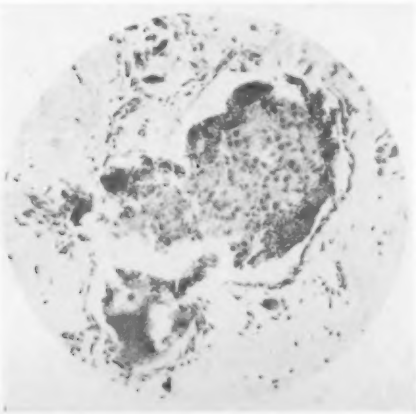


FIG. 41.—Blood spread of carcinoma. Malignant cells free in blood-stream.

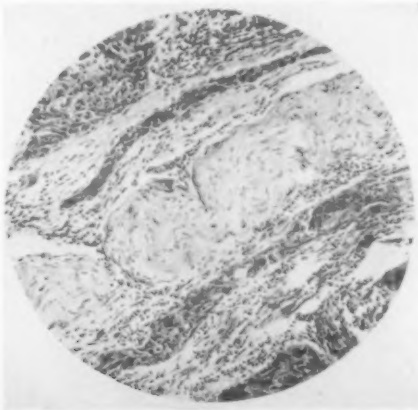


FIG. 42.—Commencing infiltration of nerve by malignant cells.

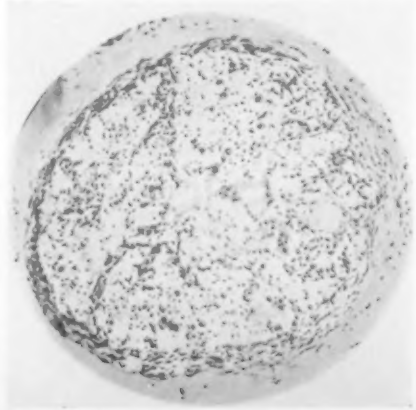


FIG. 43.—Neural invasion.

be coincident with, may precede, or may follow the excision of the mouth lesion. The gland dissection was made as complete as possible on one or other of the well-recognized block plans. A total of sixty-eight cases has been treated on these lines. They form the earliest group of the total series, and in estimating the results it is well to point out that the most recent case in the series was operated on two and one-half years ago, and that a period of ten years prior to that time is included.

I must allude to one further point before submitting the analysis. It is this—that, in order to get an accurate idea of the prognosis, we must divide the cases into two major groups: (*a*) those in which no glandular involvement was evident, on clinical or microscopical examination (forty-two cases) and (*b*) those which showed glandular involvement at the time of operation (twenty-six cases). With these somewhat numerous provisions let us now witness the results.

Looking at the question as a whole, the analysis of the sixty-eight cases is shown in the following table:

TABLE I

Total	*Cured*	*Recurred*	*Died*	*Untraced*
68	16 (23.5%)	31 (45.5%)	20 (29.4%)	1

I have tried to be reasonable and careful in the use of the all-important word "cured," and as far as is possible undue optimism has been guarded against, for the most recent case included in this group was operated on two years ago, and I think you will agree that where carcinoma of the mouth is concerned, that is a moderately good prognosis index. I need scarcely add that many of the cases are alive over a longer period of time. The death rate has been estimated as including those cases in which death might be ascribed to the operation or its immediate effects.

The results indicate that there is a proportion of cures amounting to 23.5 per cent., with a mortality rate of 29.4 per cent. as estimated over the total series of sixty-eight cases.

Let us go farther and reproduce a somewhat similar table, taking cognizance of the major distinction I have indicated, the presence or absence of glandular involvement. On this basis the results are as follow.

TABLE II

	Total	*Cured*	*Recurred*	*Died*	*Untraced*
Group A (No glandular involvement)	42	15 (35.7%)	17 (40.5%)	9 (21%)	1
Group B (Glands involved)	26	1 (3.8%)	14 (53.8%)	11 (42.3%)	

The table brings out the well-recognized truth that glandular metastasis is the touchstone by which the prognosis must be eventually judged.

So much for the general conception. Let us now look at another aspect of the question, but it may be that it conveys a lesson of practical significance. I have said that the incidence of the gland portion of the operation may be simultaneous or preceding or subsequent. I must add that in a certain number of cases no gland excision was attempted, usually because the patient was unwilling to face the ordeal. This group is included in the following summary. Analyzed on this basis the results are as follow:

TABLE III

Method	*Total*	*Cured*	*Recurred*	*Died*	*Untraced*
Local excision	25	5 (20%)	11 (44%)	8 (32%)	1
Simultaneous local and glands	19	5 (26.3%)	4 (21%)	10 (52.6%)	
Local operation first glands later	9	3 (33.3%)	6 (66.6%)		
Gland operation first local later	15	3 (33.3%)	10 (66.6%)	2 (13.3%)	

The lesson which this table would seem to convey is that, if we are to secure the lowest mortality rate, the operative procedure should be in two stages, the glandular dissection being either before or subsequent to the tumor excision. In twenty-four cases so treated the mortality figure was 8.3 per cent., while in the simultaneous group the death rate reached the deplorable figure of 52.6 per cent.

There still remains for discussion the much debated problem as to whether, if the operative procedure is to be in two stages, the tumor excision should precede the gland dissection or *vice versa*. On pathological grounds the former is probably more correct, because if we proceed to remove the glandular area while the local error remains *in situ*, a phase is apt to ensue in which cancer cells will continue to migrate by the lymphatics and thence through the cut surfaces into the tissue planes of the neck. I expect that some of us have had the disconcerting experience of witnessing the malignant cellular infiltration which is apt to follow the gland precedence two-stage operation. I cannot leave this aspect of the subject, however, without reporting what many writers have described, that from the psychological point of view the suffering and distress of a preliminary mouth operation are such that the patient resolutely refuses any further operative interference. This was the factor which led to the existence in our own series of a group of cases in which we had to be satisfied with local excision of the tumor area. There is, however, another side to the question. If we are to judge the operative procedure from the standpoint of recurrence, the smallest recurrence incidence is encountered in the one-stage or combined operation.

In discussing the results of excision methods of treatment it may seem as though I am recounting what is ancient history, and I daresay there are some who may suggest that the very mention of such mutilating procedures

is uncalled for in these days of radiotherapy, but my intention is to speak in terms of comparison and after all is said and done we live in changeful days, the pendulum may even yet swing back, and in any event for some time to come there will be cases in which the best chances of complete recovery will lie along the lines of a radical surgery.

(2) *Radium Treatment.*—This, the last section of my paper, I present with a certain measure of diffidence, for our experience has not been large, but as an experience with an individual group of cases—an experience in which we have experimented, so to speak, with the matters of dosage and method of application—the record may be of interest. For purposes of description I propose to divide the record into three epochs, early, middle, and present.

The Early Period.—When we first began using radium in the treatment of mouth carcinoma we were, I think, rather fearful of its results, apprehensive of its power as a tissue destruction agent, and relatively untutored in the technic of its application. Affected by influences such as these, we used small doses applied by the interstitial method in the form of 0.5 milligram needles, the total dosage varying from twenty to thirty milligram hours per cubic centimetre of tumor tissue. The results obtained as far as the local lesion was concerned in a series of cases were as follow:

TABLE IV

Small Dosage Group (20 to 30 mgm. hours per c.cm. of Tumor Tissue)
Interstitial Method (10 Cases)

Local lesion healed	10%
Temporary healing followed by recurrence	40%
Local lesion unchanged	20%
Local lesion aggravated	30%

These, of course, were unsatisfactory results, and consideration showed that two points were probably at fault—an insufficiency of dosage and (less definitely, perhaps) an error in the technic of administration. From this point, therefore, we entered what may be termed the middle phase of our progress, and there followed a group of cases in which a heavy radium dosage was employed (200 to 300 milligram hours per cubic centimetre of tumor tissue), while the method of application was a Stent surface applicator. Our results were certainly improved, but difficulties were encountered. There was the problem of so arranging the Stent plate that a continuous and reasonably comfortable application was secured. In this difficulty we had the assistance of an extremely ingenious dental surgeon, Doctor Robertson, who by his ingenuity overcame what seemed insuperable difficulties, but in certain situations even he had to own defeat. More disconcerting still was the degree of sloughing which followed the application of the heavy dosage. In the soft parts healing usually ensued, but in several cases the necrosis involved the bones of the jaws with disconcerting results. I submit a table which indicates the results as far as the mouth lesion was concerned:

TABLE V

Results of Treatment of Local Lesion

Surface Radiation and Heavy Dosage (200-300 mgm. hours per c.cm. of Tumor Tissue (15 Cases)

Local lesion ultimately healed, often considerable local sloughing	86.0%
Necrosis of bone leading ultimately to fatal result	6.6%
Local recurrence following temporary improvement	8.6%

Our *present phase* is one of a moderate dosage (and by that I mean an amount of 100 to 150 milligram hours per cubic centimetre of tumor tissue) applied where possible by a surface application, or, if this should prove unsuitable, by the interstitial method.

We are satisfied that we have obtained our best results where the local lesion is concerned by the method of surface application. We are unwilling to introduce needles into the tissue because we believe that in certain instances this procedure permits the entrance of infection into the surrounding tissue, and thereby stimulates cell division and tumor progress. A moderate surface dosage, with the minimum of damage and destruction to the part, appears to offer the best prospects of a satisfactory result.

There is considerable variation in the way in which tumors respond to radium therapy. Broders recognized this peculiarity in his classification, and he has alluded to the fact that the undifferentiated type (Group IV), is that which shows the quickest response to radio-active substances. I believe it will ultimately be found that the degree of cell resistance is in relation to the amount of keratin which the cell contains, that full keratinization, with its associated cell next formation, is a phase of cell change which is peculiarly resistant to radiotherapy.

The Problem of the Glands.—The problem of the cervical glands is a difficult one. The efficacy of radium in this situation is open to serious question, and for myself I feel that the most satisfactory way of dealing with the lymphatic field is to submit it to a radical block dissection elimination. If there is already such glandular invasion that radical removal is out of the question, we must be satisfied with the method of interstitial radiation, using a large dosage.

General Procedure.—I conclude with an outline of the procedure we at present adopt in an early case of buccal carcinoma. The preliminary treatment implies the correction of all areas of infection within the mouth; all the teeth are removed except such as may be required for the fixation of the dental plates, the gums are painted night and morning with equal parts of tincture of iodine and tincture of aconite, and appropriate mouth-washes are used. At this time a suitable dental plate is made by the dentist. When the interior of the mouth is sufficiently clean, the radium carrying plate is applied, it being so arranged that the tumor area and a surrounding segment of half an inch are submitted to the influence of the radium; by means of a lead, or preferably a platinum, screen the healthy portions of the mouth are protected from the influence of the Beta rays. The plate is kept *in situ* until

a sufficient dosage has been secured; it should be removed for meals or other special purposes, but a careful note should be kept of the time period which such removal may imply. As I have already said, if the difficulties of surface application should prove insuperable, we employ the method of interstitial radiation.

When the surface lesion is healed the glandular tissue on the affected side is dissected. I believe it is inadvisable to do the glandular operation before the mouth lesion is corrected, the reason being that if we carry out the neck dissection while the primary focus exists, we are submitting the patient to the risk of a malignant infection of the cellular tissues of the neck along the lines of the cut lymphatics. It is probably particularly dangerous to practise a glandular dissection during the early stages of radium application to the local lesion, for at this time malignant cells are passing from the periphery of the tumor to the related lymphatics. In the course of the glandular dissection we introduce thirty to forty milligrams of radium underneath the posterior portion of the digastric muscle, this being an area in which the most thorough dissection is liable to be incomplete, and the insertion of the radium constitutes a greater degree of security. Ten days after the first glandular dissection the tissues of the opposite side are removed.

In a small proportion of cases the technic concludes with the application, after all wounds are healed, of a Columbia paste of Stent collar carrying a large surface dosage of radium. I confess I am doubtful about the efficacy of this last procedure, but we have occasionally employed it.

Thereafter the patient reports at monthly intervals for a period of six months, and then at intervals of three months until two years have elapsed.

I recognize that my remarks regarding radium therapy are indefinite but I have attempted to present the procedure which we adopt. I have not alluded to end-results because insufficient time has elapsed to justify any opinion.

We feel that there is probably no fixed and uniform carcinoma dose—that if the tumor is to be affected a certain minimum radiation is necessary but on the other hand a maximum dose must not be excudia or if we are to avoid injury to the normal tissues.

In conclusion, I want to say how much I owe in the preparation of this paper to my clinical assistant, Mr. Eric Mekie—the bulk of the pathological work has been done by him. I also very gratefully acknowledge the great amount of technical assistance I have had from Mr. Smith and his assistants in the Department of Clinical Surgery.

THE PATHOGENESIS AND SYMPTOMS OF CHRONIC OBLITERATIVE APPENDICITIS

By J. Shelton Horsley, M.D.
of Richmond, Va.,
and
Harry J. Warthen, Jr., M.D., by invitation
of Baltimore, Md.

Chronic appendicitis is usually divided into three classes—catarrhal, interstitial, and obliterative. As to the first two classes, the catarrhal and the interstitial, there are a variety of opinions, some even doubting their existence. We will not discuss them, but concern ourselves with obliterative appendicitis.

Since the early days of appendicitis, various writers have commented upon that type in which the lumen of a portion or all of the appendix has been slowly obliterated. This kind of appendicitis has been called by various names, such as "appendicitis granulosa," "fibroid degeneration of the appendix," "appendicitis irritans," "protective appendicitis," and "chronic obliterative appendicitis." There were different explanations of this condition. Some, as W. J. Mayo, Robert T. Morris, Ribbert, and others, placed chronic obliterative appendicitis as an involutionary and physiological phenomenon. Others, as Senn, Fitz, and MacCarty, thought it was inflammatory, beginning in the mucous membrane as a superficial ulceration, in the deeper layers as an interstitial process, or as a lymphatic infection.

It is not our purpose to quote fully the literature on this subject, which is quite voluminous and which can be readily consulted. However, some of the opinions must be presented to indicate the status of this disease.

MacCarty and McGrath pointed out that the process of obliteration of the lumen of the appendix occurs during all ages, from five years to old age, and that its activity is greatest between birth and forty years of age. The average age at which the lumen is found to be completely obliterated is 34.6 years for appendices removed for appendicitis, and 39.1 years for appendices removed during operation for cholecystitis. They state that the tip may be obliterated at five years of age, and the total lumen at ten years of age. Either complete or partial obliteration of the lumen was found to occur in 23.5 per cent. of 1,005 specimens removed for appendicitis alone, and 22.8 per cent. of 5,000 specimens removed for appendicitis associated with other abdominal conditions. The oldest patient with total obliteration was sixty-nine years of age, and the youngest ten.

MacCarty calls attention to the occurrence in obliterative appendicitis of carcinoma of the appendix, which apparently is due to a chronic inflammatory process. He states that 90 per cent. of carcinomas of the appendix are found in partially or completely obliterative appendicitis.

According to Pfeiffer, obliteration of the lumen of the appendix occurs as a result of certain types of acute appendicitis in which the mucosa has become completely gangrenous, without gangrene of the outer coats. Such conditions, however, must be rare unless accompanied by acute symptoms. It is difficult to imagine complete gangrene of the lining of the appendix without sufficient surrounding reaction to cause very

marked symptoms, even though the peritoneal coat may not be actually involved in the gangrenous process; though histories of previous severe attacks of colic or abdominal pain are sometimes so indefinite that the possibility of such an occasional occurrence cannot be denied.

Eli Moschcowitz maintains that there is no pathological evidence of involution of the appendix or catarrhal inflammation of the appendix. Chronic appendicitis, according to Moschcowitz, usually represents the healed result of an acute lesion.

According to Ribbert, the first signs of obliteration may occur in the fifth year of life, while in more than 50 per cent. of patients over sixty years of age some stage of obliterative appendicitis is seen.

Hugh Cabot speaks of chronic appendicitis as the scapegoat of abdominal surgery. He says we must not forget the fact that appendices are larger in children and smaller in old age, relatively speaking. In old age there is some process going on which shrinks the organs.

This change that Cabot mentions, however, is not confined to the appendix; the liver, for instance, is relatively much larger in the new-born infant than in an adult, and the thymus almost disappears after adolescence, while the prostate tends to enlarge in the old.

P. Masson, of Lyons, France, says that when an inflamed appendix becomes blocked, the nerve terminals may proliferate and form an actual neuroma. Masson has seen neuromas of the sympathetic fibres enclosed in a sheath and this in a shell of muscle. The contraction of the muscular shell may set up reflex action as with a neuroma after an amputation and give symptoms. This neuroma formation was found in all but one of his ten cases of obliterative latent appendicitis.

To show the status of the opinion about obliterative appendicitis, Royster, in his monograph on appendicitis, says: "In the midst of these varying views, it might be safe to conclude that obliteration of the appendix may result from a chronic pathological process, or from a physiological atrophy. Whether any clinical differences between these two types are distinguishable is difficult to determine."

The advocates of the theory of physiological involution as the explanation of obliterative appendicitis say that this condition is found more often in elderly people than in the young, and that it usually gives few, if any, symptoms. Histological examination may show complete obliteration of the lumen, but occasionally there is a thin growth of a superficial epithelium along the almost completely obliterated lumen. This, it is argued, is an evidence of a physiological process, otherwise the epithelium would have disappeared completely. This epithelium, however, is not often found, and, when present, would seem merely to indicate that epithelium may spread over a healing surface. The epithelialization of a raw surface is a common phenomenon. We have noticed that even in experimental reconstruction of the common bile-duct in a dog with a transplanted section of a vein there is a tendency for the epithelium of the bile-duct to grow over the venous transplant.

The fact that obliterative appendicitis is found more frequently in the old than in the young is not proof that this condition is physiological and involutionary. A worn bearing in an automobile is more common in old cars than in new. The longer a biological machine, such as the human body, exists, the more probability there is of its organs becoming in some way affected. It has been said by Osler and others that in a large majority of necropsies of those dying past forty years of age, evidences of healed or arrested tuberculosis are

found. The argument, therefore, might be equally well sustained that tuberculosis is a disease of old age.

The specimens which we have examined have shown a range from slight obliteration at the tip of the appendix, the rest of the appendix being almost normal, to obliteration of its entire lumen. There are almost all stages between these two extremes, and in more than half (58.7 per cent.) of those without complete obliteration some evidence of inflammation is found on the proximal side of the obliteration. This seems to indicate that the process of obliterative appendicitis usually begins in the tip of the appendix as an inflammation and may be limited to this region, or, if the inflammation continues, may gradually proceed toward the base. The inflammation that produces this lesion is comparatively mild. It is well known that certain types of inflammation predispose toward cicatricial contraction more than others. Hepatitis, for instance, may result in cirrhosis in which almost all of the parenchyma of the liver is strangled by the contracting scar tissue; but all types of hepatitis do not lead to cirrhosis. Some of them produce abscesses; some, marked parenchymatous degeneration; while others appear to subside, leaving no trace. This inflammation of chronic obliterative appendicitis chiefly affects the mucous membrane, and usually begins at the tip of the appendix, probably because it forms a cul-de-sac, and with the stagnant fæces acts as an incubator.

Upon the process of chronic obliteration a typical acute appendicitis may be imposed. We have not infrequently seen an acute appendicitis with violent inflammation added onto an obliterative process.

The absence of symptoms or the comparatively mild clinical signs and symptoms induced by obliterative appendicitis are considered an argument for the involutionary process. The chief cause of pain in appendicitis appears to be pressure, doubtless along with a sensitizing of the nerves from the congestion and infection. But in chronic obliterative appendicitis none of these conditions is conspicuously present. Certainly the inflammation is accompanied by very little hyperæmia, and there is no acute pressure. As the ulcerative process slowly proceeds toward the base of the appendix it leaves a healing mass of tissue and scars in its wake. There is no obstruction to appendicular drainage, and there is no occasion for unusual pressure. This process involved in chronic obliterative appendicitis may, rarely, begin in some other regions of the appendix, as in the base or in the middle. When a stricture occludes the lumen of the appendix and leaves the distal portion unobliterated, symptoms may arise quickly. If there is infection, the lack of drainage from the appendix may cause a typical acute appendicitis. If there is but little infection, the products from the mucous membrane cannot be drained into the cæcum by the natural route, and there may be a gradual accumulation of mucus, causing cystic dilatation.

Strictures of the appendix doubtless have several etiological factors, the most common being a local acute or subacute inflammatory lesion, but it seems logical to expect that the process of obliterative contraction of the lumen usually beginning at the tip may occur at other parts of the appendix. We

have observed a case (Figs. 1 and 2) in which this obliterative process began at the base of the appendix instead of at the tip. (Mrs. J. P. T., Case No. A1828.)

The obliterative appendicitis found in the aged has probably existed for years. It has been definitely shown that chronic obliterative appendicitis may be present in a patient five years of age. In one of our patients, seventeen years of age, the lumen of the appendix was completely obliterated. It is not an involution process or a respecter of age as, for instance, wrinkling of the skin, atrophy of the uterus, or other changes common to increasing age or to lack of function. In the young the lymphatics are abundant and the tissues juicy. Cancers in the young are usually rapidly growing and not often of

FIG. 1.

FIG. 2.

FIGS. 1 and 2.—Mrs. J. P. T. (A1828), aged forty-five years. Operation October 10, 1929. The appendix was five and one-half centimetres long. The distal three-fourths were about normal size. The proximal fourth was sharply contracted, with the area of contraction beginning at the base. The lumen was greatly contracted in the proximal fourth and had almost disappeared. The lumen of the rest of the appendix was larger, but was somewhat smaller than normal. There was some congestion of the mucosa, particularly in the distal portion. This represents obliterative appendicitis near the base.

the scirrhous type. The more highly classed tissues, such as the epithelial tissues, are more likely to survive and to repair under the conditions of youth with excellent lymph circulation and blood supply than in old age. It seems probable, then, that infection in the young would be more rampant and less likely to go the more conservative methods of slow inflammation than in the aged.

Hellwig, in writing upon obliteration of the vermiform appendix, says: "An appendix with complete obliteration will not undergo inflammation again and its removal will not relieve the patient of his symptoms. An appendix with partial obliteration, on the contrary, is disposed to recurrent inflammation, because the stenosis of the non-occluded portion and the fibrosis of the muscle layers favor retention of its contents and bacterial invasion of the mucosa."

The statement of Hellwig, which appears to represent the opinion of many surgeons, that the removal of an appendix with a completely obliterated lumen will not relieve the patient of his symptoms, is contrary to our clinical experience. It must be recalled that the same lesion in different individuals will often produce different symptoms. A neuroma in one patient may be exquisitely sensitive, while a neuroma of a similar histological type in another may give no symptoms or very slight discomfort. This should not mean that, because one person with a neuroma complains little or none at all, the one who does suffer should go unrelieved.

A study of 273 cases of appendicitis with the lumen of the appendix partially or completely obliterated which have been operated upon at St. Elizabeth's Hospital, Richmond, Virginia, from January 1, 1922, to January 1, 1932, gives interesting information on some of these mooted points. During that decade there were removed at this hospital 1,713 appendices.* The

FIG. 3.

FIG. 4.

FIG. 3.—Mrs. N. L. (7678), aged thirty-two years. Operation March 28, 1923. The appendix was seven and one-half centimetres long, deeply congested. The tip was nodular, firm and white. The mucosa was deeply congested throughout and in small patches showed necrosis. The obliterated portion at the end was about one centimetre in length. The wall was thick, and the lumen had almost disappeared. There was apparently no mucosa. The patient had marked acute appendicitis.

FIG. 4.—Mrs. R. (A39), aged thirty-five years. Operation October 31, 1925. The appendix was six and one-half centimetres long, thickened at the tip and near the tip the lumen was almost obliterated. Adjoining this the mucosa showed an ulcer which extended well through the superficial portion of the mucosa. Elsewhere the mucosa was apparently normal.

* Two cases of cancer of the appendix, 368 cases of subacute appendicitis, 56 cases of acute appendicitis with spreading or general peritonitis, 55 cases of acute appendicitis with perforation, 35 cases of acute appendicitis with abscess, 534 cases of acute appendicitis, and 663 cases of chronic appendicitis or normal appendices many of which were removed incidentally during operations for other conditions.

proportion of partially or completely obliterative appendicitis to all the appendices removed is 15.39 per cent.

The specimens reveal many stages, from beginning obliteration at the tip (Figs. 3 and 4) to a complete obliterative appendicitis, the appendix being converted into a small cord without any lumen, or with merely a trace of brownish tissue around a minute lumen. Cases with mere thickening at the extreme tip of the appendix, without some closure of the calibre of the appendix near the tip, are not classed as obliterative appendicitis, as this condition may result from a congenital thickening or from an acute local inflammation that does not tend to extend. However, it would be difficult to differentiate some of these cases from early obliterative appendicitis. In eighty-nine cases there was complete obliteration

FIG. 5. FIG. 6.

FIG. 5.—Miss F. W. (A166), aged thirty-four years. Operation December 18, 1925. The appendix was eleven and one-half centimetres long. For about two centimetres at the tip the appendix was smaller than elsewhere, was firm and hard, and the lumen had entirely disappeared. There was a superficial ulcer on the proximal side of this area. This was definitely marked off for about one centimetre. The tip was firm and the mucosa had entirely disappeared. Between this region and the ulcer, for about one and one-half centimetres, the mucosa was atrophied. The wall was very thick. It appeared to be undergoing the process of obliteration with the very distal mucosa completely obliterated, the adjoining mucosa almost destroyed, and next to this an ulcerated area of otherwise normal mucosa.

FIG. 6.—Mrs. M. J. C. (9529), aged thirty-five years. Operation May 8, 1925. The appendix was six and one-half centimetres long. At the tip was a thickened area in which the mucosa had disappeared for a distance of about one-half centimetre. On the proximal side of this the mucosa was stippled and slightly congested and swollen. This extended to the junction of the distal and middle thirds.

of the lumen. Subtracting this from the total number of cases of obliterative appendicitis leaves 184 with incomplete obliteration. There was noted either superficial ulceration or hyperæmia confined to the mucosa adjoining the obliterative portion of the appendix or most evident in this region in sixty-one of these 184 cases (Figs. 4, 5, 6 and 7), and erosions or hyperæmia diffusely placed throughout the mucosa as well as near the obliterative portion in forty-seven cases. In seventy-six cases no signs of hyperæmia

or ulceration in the mucosa were observed at the time of operation. This does not necessarily mean, however, that this process had not been present at some previous time. With such a large proportion (108 out of 184 cases, 58.7 per cent.) showing

FIG. 7.—Mr. O. E. L. (A2489), aged forty-two years. Operation, February 3, 1928. The appendix was eight centimetres long. The distal end for about one and one-half centimetres was entirely occluded. The mucosa adjoining this was eroded, more marked at the junction with the occluded portion. The mucosa in the proximal portion was apparently normal. Photomicrographs of this specimen will be shown.

evidences of superficial ulceration and inflammation adjoining the obliterated portion and with only that portion of the mucosa next to the obliterated portion involved in sixty-one cases, it seems probable that this inflammatory process had existed at some time in all of these 184 cases but in those in which it was not obviously present at the time of operation the process was in abeyance. We know that acute inflam-

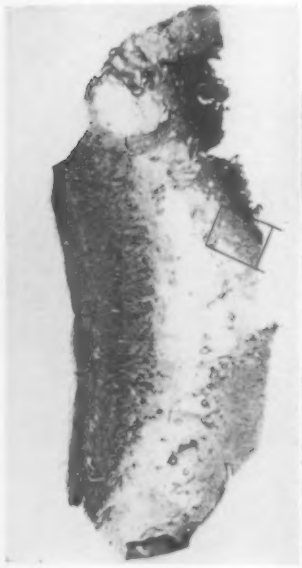


FIG. 8.

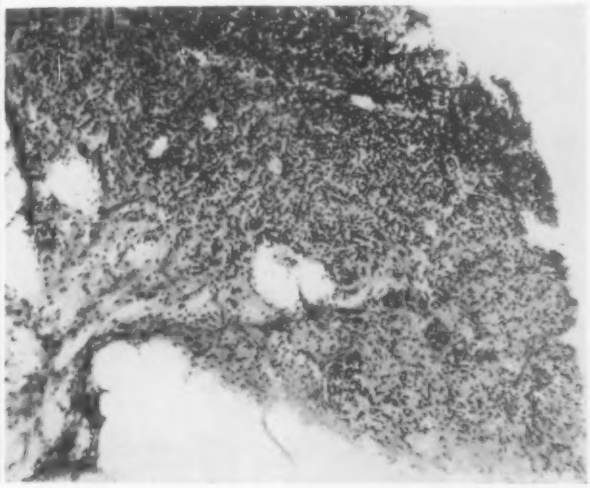


FIG. 9.

FIG. 8.—Longitudinal section of appendix shown in Fig. 7, (x 10), showing area of congested mucosa at the line of demarkation with the obliterated portion.

FIG. 9.—Blocked-out area of the preceding figure (x 100). To the left and above is the infiltrated area containing some remnants of mucosa and much leucocytic infiltration, gradually blending into the obliterated portion to the right and below.

mation of the appendix, of the gall-bladder and of other organs or tissues may pass off and leave but little if any trace of the attack.

All of these appendices have not been studied histologically, but a histological study of some of them is interesting. A cross-section of the obliterative portion pre-

sents a fairly uniform picture. The muscular coat is usually well preserved. In the lumen there is a mass of irregular tissue, much of which seems reticulated containing some fat and showing ordinary connective or scar tissue, but no epithelium. In all of the specimens histologically examined there is evidence in the obliterative portion of old inflammation, such as young fibroblasts or leucocytic infiltration. A section including the junction of the obliterated lumen with the proximal appendicular mucosa which is inflamed shows a rather sudden transition into acutely inflammatory tissue, as shown by marked leucocytic infiltration, and some destruction of the epithelial cells. This usually gradually fades off farther toward the base into what may be considered normal appendicular tissue. Typical views of this process are shown in the photomicrographs, Figs. 7, 8, 9, 10, 11, 12, 13 and 14.

As for symptomatology, it is well known that the symptoms even of acute appendicitis may sometimes be puzzling, especially when the appendix is not

FIG. 10.

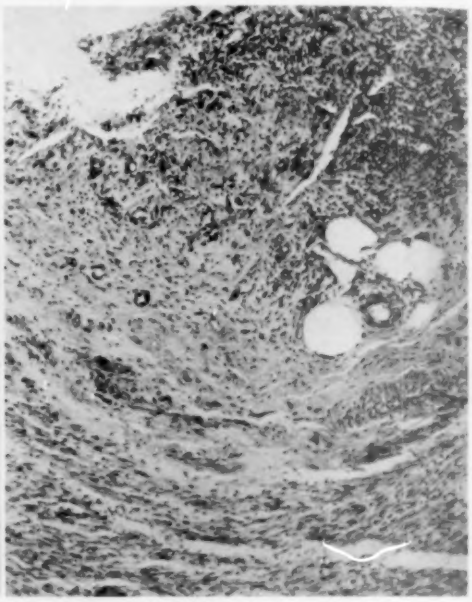


FIG. 11.

FIG. 10.—Cross-section of obliterated portion at the tip of the appendix shown in Fig. 7. (x 20.) The mucosa had disappeared. The muscular coat was fairly well preserved. Most of the lumen had been filled with what appeared to be connective tissue with interstitial areas, probably occupied by fat.

FIG. 11.—Higher power of area blocked out in the preceding section. (x 100.) Note the leucocytic infiltration of the tissue filling the cavity, and the comparatively normal muscular coat.

in its usual location. With obliterative appendicitis the type of pathology has much to do with the symptomatology. The great majority of appendices are located with the base under McBurney's point, and in obliterative appendicitis as in acute appendicitis the point of tenderness is usually over this point, but the tenderness from the appendix may be in the cul-de-sac or on the left side, or in the upper right hypochondriac region, depending upon its location.

In partial obliterative appendicitis, the symptoms cannot be necessarily attributed solely or even chiefly to the obliteration, because, as is well known, acute symptoms or even rupture may occur in the proximal portion of the

FIG. 12.

FIG. 13.

FIG. 14.

FIG. 12.—Dr. T. W. W. (A6232), aged thirty-seven years. Operation February 28, 1931. Appendix was ten and one-half centimetres long and obliterated throughout except for a small portion at the base. Section shows a small remaining mucosa near the base at its junction with the obliterated portion. (x 15.)

FIG. 13.—Enlarged area of the preceding figure that has been blocked out, showing leucocytic infiltration being more dense toward the base where normal mucosa existed. (x 60.)

FIG. 14.—Higher magnification of blocked-out area in preceding figure, showing marked leucocytic infiltration, decreasing toward the obliterative portion. (x 100.)

appendix when much of the distal part has been obliterated. Naturally, in such a case the symptoms are those of any other type of acute appendicitis, regardless of what has happened to the distal part of the appendix.

There are many individuals who have other pathological lesions in the abdomen that dominate those of obliterative appendicitis and there are others whose sensitive threshold is so high that a moderate amount of pathological lesions may create no symptoms.

There are in our series eighty-nine cases of complete obliterative appendicitis, but only in thirteen of these cases was an operation done solely for appendicitis with no other demonstrable pathological condition existing at the time except local adhesions in some of these cases. While this group is small, it was felt that following them up carefully would be indicative of the symptomatology of chronic obliterative appendicitis. The positions of these appendices, which were not identical in any two cases, may have had something to do with the difference in symptoms.

Of these thirteen patients with complete obliterative appendicitis, seven were men and six were women. All made a satisfactory operative recovery. The average age was thirty-five and one-half, the youngest seventeen and the oldest fifty-three years. The operations were done between October 14, 1923, and September 7, 1931. In eight cases the symptoms complained of before the appendix was removed were entirely relieved. In two cases the symptoms were not relieved, though one of these patients had hypertension and died six years later of apoplexy. In three cases the original symptoms were partially relieved but other symptoms appeared. All had pain on pressure over the region of the right iliac fossa, some at the lower portion and some at the upper, but most of them within two or three inches of the anterior-superior spine of the ilium. Most of the patients had suffered for months or years with recurrent attacks of abdominal pain, with "gas," "indigestion," constipation and a rather vague consciousness of abdominal discomfort. One patient (Mrs. J. B., No. 8172) had a typical attack of acute appendicitis and was operated upon as an emergency. She was completely relieved of her symptoms.

As this group is small, a brief abstract of each case is given.

Case I.—Mr. R. N. C. (Case No. 8078), aged thirty-one years. Two years ago, six months ago, and for the past thirty hours the patient had pain in the right lower quadrant, with nausea and vomiting. There were no digestive disturbances between attacks. Appendectomy was done October 14, 1923. The appendix was 7.5 centimetres long, smaller than normal, slightly congested, with no adhesions. On section it seemed to be practically a solid cord to within a half-inch of the base where there was a small lumen. In this region the mucosa was atrophied and thin. The patient had hypertension. His symptoms were not entirely relieved by the operation. He died January 3, 1929, of apoplexy.

Case II.—Mrs. W. L. A. (Case No. 8106), aged forty years. The patient had had indefinite pain in the abdomen, with constipation and "gas," for the past fifteen years. There was pain on pressure over the right lower quadrant of the abdomen. Appendectomy October 24, 1923, with division of Lane band. The appendix was 6.25 centimetres long, universally covered with adhesions, and had a short mesoappendix attached.

On section it seemed to have a completely obliterated lumen. Patient reported in April, 1932, complete relief from symptoms.

Case III.—Mr. E. A. S. (Case No. A432), aged thirty-five years. The patient had tenderness and indefinite pain which was occasionally referred to the right groin and upper right thigh. The symptoms began eighteen months previously, with some tendency to constipation. For the past month there had been a dull pain in the right abdomen and the patient was always conscious of it. Physical examination showed slight rigidity of muscles of the right lower quadrant, and very slight tenderness on deep pressure. Appendectomy, April 3, 1926. The appendix was densely adherent, eleven centimetres long, and smaller than normal. (Fig. 15.) At the tip the appendix had narrowed down to a filament. This was removed without the peritoneal covering. This filament gradually merged into the large portion of the appendix which even then was not of normal size. The base was somewhat funnel-shaped and consisted of the appendix and the immediately adjacent cæcum. On section the lumen seemed to be entirely obliterated up to a centimetre of the base, where the mucosa showed a moderate amount of congestion. Sections of the obliterated portion did not even show the usual brown centre where the mucosa had disappeared. The patient reported April, 1932, complete relief from symptoms.

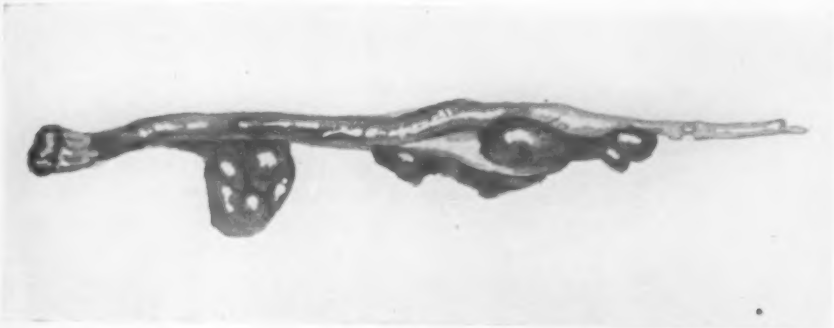


Fig. 15.—Mr. E. S. (A432), aged thirty-five years. Operation April 3, 1926. The appendix was eleven centimetres long, smaller than normal. The tip had narrowed to a filament. This area was removed without the peritoneal covering. From the tip toward the base the appendix tended to become larger. On section the lumen appeared to be obliterated throughout to within about one centimetre of the base, where it flared out into the cæcum.

Case IV.—Miss L. M. (Case No. A657), aged fifty years. One month before admission, following an attack of influenza, the patient had a chill, nausea, and tenderness in the abdomen most marked on the right side. This persisted until operation, May 3, 1926. The appendix was 8.5 centimetres long, somewhat smaller than normal. There were no adhesions or congestion. The appendix was very firm. On section the lumen was practically obliterated throughout. Patient reported April, 1932, complete relief from symptoms.

Case V.—Mrs. W. L. B. (Case No. A2582), aged thirty-three years. For four years before admission the patient had been having recurring attacks beginning with cramps in the "pit of the stomach." She would have a sensation of fullness, become nauseated but could not vomit. She had hot and chilly sensations. She would then get better and the pain in stomach would leave, but there would be a dull ache and soreness in the lower abdomen on the right side. Her last attack was five months before admission; since then there had been definite tenderness in the right lower quadrant. On physical examination there was tenderness on pressure in the right hypochondriac region, with some muscle spasm over the right iliac fossa. Appendectomy March 6, 1928. The appendix was somewhat adherent in the mesenteric border, 10.5 centimetres long, smaller than normal, and had a very fat mesentery. There was no congestion. On section the appendix seemed to be completely obliterated from the tip

to the base, where there was a small lumen and thin mucosa. Patient reported April, 1932, that she was unimproved.

CASE VI.—Mr. J. C. C. (Case No. A2614), aged twenty-seven years. For the past two years he had had attacks of "indigestion" and had had a dull ache in the region of the appendix which had been fairly constant. He had not been constipated. Three days before admission the patient had cramp-like pains in the region of the umbilicus, which seemed to radiate upward. He was nauseated and vomited. The cramp subsided but left a dull ache in the right lower abdomen. Abdominal examination showed moderate tension with no distention, and distinct tenderness on deep pressure over the right iliac fossa. Appendectomy March 15, 1928, with division of Lane band. The appendix was 3.5 centimetres long, smaller than normal, of whitish color, and presented no evidence of adhesions. On section it appeared to be obliterated throughout, even at the base, and the mucosa had disappeared. Patient reported April, 1932, complete relief from symptoms.

CASE VII.—Mrs. H. M. (Case No. A2681), aged forty years. The patient had an attack of acute appendicitis twenty-four years previously. Since then she had been having recurring attacks of indigestion with generalized pain, some nausea and soreness in the right iliac fossa. These attacks had been closer together for the past several months and she had had a more or less constant pain in the right side. There was some gas and distention after eating. Constipation was present. Physical examination showed marked spasm and some tenderness in the right iliac region. Appendectomy April 5, 1928. The appendix was five centimetres long, smaller than normal, slightly congested, and presented marked evidence of adhesions. On section it was firm and cord-like throughout. Patient reported April, 1932, complete relief from symptoms.

CASE VIII.—Miss A. C. (Case No. A3327), aged seventeen years. Four days before admission the patient had pain in the right side which remained in the same location, growing increasingly worse. On the third day she became nauseated and vomited. She had had previous attacks of the same kind. Physical examination showed tenderness in the right lower quadrant with muscle spasm of the right rectus muscle and over McBurney's point. Appendectomy September 17, 1928. The appendix was nine centimetres long, smaller than normal, markedly adherent throughout. It was firm and cord-like. On section it seemed obliterated throughout. Patient reported April, 1932, complete relief from symptoms.

CASE IX.—Mr. C. F. J. (Case No. A3934), aged thirty-two years. The symptoms began about eight years ago, with indigestion and pain which would seem to radiate to the right lower quadrant. He had been having recurrent attacks of indigestion, gas and constipation over a period of six years. About a month before admission the patient had some neausea, and pain in the right lower quadrant. Two and a half years previously there had been an attack of jaundice, when the patient remained in bed for two weeks and was jaundiced for about six weeks. Physical examination showed the abdominal muscles with increased tone, and slight tenderness in the region of the right iliac fossa. There was some tenderness in the region of the gall-bladder. Appendectomy, and exploratory of upper abdomen, March 23, 1929. The gall-bladder appeared normal. The appendix was four and one-half centimetres long, presented evidence of adhesions near its base, and was not congested. It was quite firm. The tip was larger than elsewhere. On section the lumen seemed to be almost obliterated throughout. The wall was thick and presented the appearance of obliterative appendicitis. Patient reported April, 1932, that he had been improved by the operation but still had some symptoms.

CASE X.—Mrs. J. B. (Case No. 8172), aged fifty-three years. The patient was admitted to the hospital as an emergency. Ten days before admission there had been a dull pain over the entire abdomen. This localized in the right lower quadrant the day before admission. There was nausea with no vomiting. There was a history of previous attacks. The patient was not constipated. Physical examination shows rather

acute tenderness and decided muscle spasm in the right iliac fossa. The point of tenderness seemed to be about half-way between the umbilicus and the anterior-superior spinous process. Appendectomy, June 16, 1929. The appendix was seven and one-half centimetres long, somewhat smaller than usual and larger in the distal half than in the proximal half. Near the tip there was slight congestion, but the appendix throughout was firm and almost white in color. On section the mucosa seemed to have disappeared and it presented the typical appearance throughout of obliterating appendicitis. Patient reported April, 1932, complete relief from symptoms.

Case XI.—Mr. H. G. S. (Case No. A4890), aged forty-six years. Several years ago the patient had an attack of very severe pain in the right lower quadrant, accompanied by nausea and vomiting. He was confined to bed. There were two similar attacks later. About two months before admission he began to have a dull ache in the right side; he was confined to bed for a while; the pain was usually dull but at times there were sharp, stabbing pains which radiated across the lower abdomen.

Fig. 16.

Fig. 17.

Fig. 16.—(Case XII.) Mr. O. A. R. (A6086), aged thirty-three years. Operation January 26, 1931. The appendix was eleven centimetres long, smaller than normal, and obliterated practically throughout except for a short distance near the base. Longitudinal section at the base shows leucocytic infiltration of the mucosa near the obliterated portion. (x 18.)

Fig. 17.—Higher magnification of the blocked-out area in the preceding figure, showing the mucosa at the junction with the obliterated portion. (x 100.)

He had been unable to work for some time. On physical examination there was definite tenderness over the upper portion of the right lower quadrant. Appendectomy January 3, 1930. The appendix was six centimetres long, somewhat smaller than normal, and quite firm. It presented evidence of almost universal adhesions. On section the lumen was almost obliterated throughout. Patient reported April, 1932, complete relief from symptoms.

Case XII.—Mr. O. A. R. (Case No. A6086), aged thirty-three years. (Figs. 16, 17, 18 and 19.) The symptoms began about ten months before admission, and lasted for six weeks, with cramping pains in the epigastrium and sometimes in the right side. Then there was a remission until seven months later and this time the pain was more localized in the right side. There were several attacks following this, and two or three days before admission he had had an attack of epigastric pain accompanied by

nausea and vomiting, with pain gradually localized in the right lower quadrant. On physical examination there were slight pain and discomfort in the epigastric region, and some pain on deep pressure in the right iliac fossa. Appendectomy January 26, 1931. The appendix was adherent, eleven centimetres long, rather smaller than normal, somewhat congested and firm. On section the lumen seemed to be almost obliterated, closed except at the base. Patient reported April, 1932, that he was improved by the operation, but still has some symptoms.

CASE XIII.—Dr. C. G. F. (Case No. A6925), aged twenty-five years. The patient had been feeling generally below par for the past week, but had not completely recovered from a head injury with anaphylactic shock from tetanus antitoxin several months earlier. He complained of severe colicky pains over the abdomen and definite arthritic pains in the right knee. The urine was cloudy and contained some blood. The abdomen showed generalized distention with very definite pain on moderate pressure in the left lower quadrant and left upper quadrant, and, to a less extent, in the right

FIG. 18.

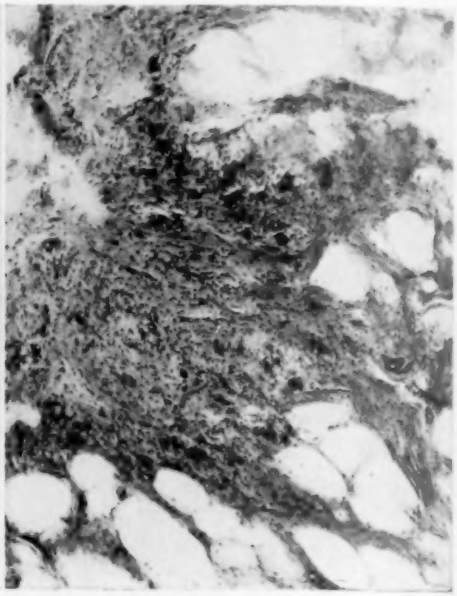


FIG. 19.

FIG. 18.—Cross-section of appendix of Mr. O. A. R. (A6086). The muscular coat is fairly well preserved, the lumen occupied by trabeculated connective tissue resembling that in Figs. 10 and 11. (x 18.)

FIG. 19.—Blocked-out area in the preceding figure, showing infiltration with inflammatory products of tissue occupying the former lumen. The surrounding area was apparently filled with fat; the lumen had disappeared. (x 100.)

lower quadrant. The pain later definitely localized over the appendix. Appendectomy and separation of adhesions to the ascending colon, September 7, 1931. The appendix was eight centimetres long, smaller than normal and congested. It was somewhat adherent to the cæcum. On section it presented the appearance of obliterative appendicitis throughout. The peritoneal coat was markedly congested. The patient reported April, 1932, that he is improved and has had none of the attacks of pain which he had before operation, but has some gastro-intestinal symptoms resembling those of colitis.

CONCLUSIONS.—(1) Chronic obliterative appendicitis is the result of a chronic inflammatory process that tends to destroy the mucosa and obliterate the lumen of the appendix. It may last for many years.

(2) It may exist in any stage, from involvement of a small portion at the tip to complete obliteration of the entire lumen of the appendix.

(3) It may be found at any age, from five years upward, but is more frequent in the elderly, probably because they have had longer opportunities for attacks of inflammation.

(4) Acute appendicitis or even rupture of the appendix may occur in an appendix that has been partially obliterated.

(5) In a small series of cases (thirteen) in which there was completely obliterative appendicitis and in which the operation was solely for appendicitis, there were definite symptoms before operation. Eight of these patients have been entirely relieved of their symptoms, three of them have been partially relieved, and two were not relieved. Complete obliterative appendicitis may produce marked symptoms which may be relieved by removal of the appendix.

(6) While a complete obliterative appendicitis seems incapable of producing a serious peritonitis, it may cause discomfort that can be relieved only by operation. An accurate diagnosis of chronic obliterative appendicitis is difficult until the abdomen is opened, and right-sided lower abdominal pain should be carefully investigated before any such diagnosis is ventured. Ureteral lesions, a small hernia, ulcers in the terminal ileum or cæcum, arthritis or lesions of the spine, and disease of the sacro-iliac joint, should be considered before assuming a clinical diagnosis of chronic obliterative appendicitis.

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ACUTE APPENDICITIS—A BRIEF CRITICISM

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The mortality rate in acute appendicitis is appalling. The degree of professional dissatisfaction is indicated by the fact that, within the last two years, over 500 papers on this disease have been published. Jeff Miller[1] aptly terms the high death rate "a menace to humanity, a disgrace to the medical profession and a challenge to us who claim to practice the science and art of surgery." The medical profession has as yet never failed to fight any encroachment upon their right to serve humanity.

Willis,[2] in 1926, reported a marked increase in mortality rate averaging 14.5 per cent. per 100,000, 80 per cent. of all deaths occurring before the fiftieth year, or during the productive period of life. He emphasized the fact that "deaths from appendicitis equal all those from salpingitis, pelvic abscess, surgical diseases of the pancreas, spleen, thyroid, gall-stones, gastric and duodenal ulcers."

Coller and McRae,[3] after a most careful statistical study, found a steady increase in fatalities in the last twenty years. In 1926, over 18,000 died as a result of appendicitis.

Bankhead Banks[4] states that the mortality rate was 50 per cent. higher in 1928 than in 1915, and that prior to the age of fifty, four times as many die from appendicitis as from cancer.

John B. Murphy,[5] in 1894, soon after perityphlitis and bowel-block had merged into perforated appendicitis, wrote: "There is no palliative excuse for a mortality of 10 per cent. in appendicitis. It is so common and so important a condition that the indications for its treatment should and must be a matter of common knowledge among doctors and laymen."

A cross-section of an exhaustive statistical review shows a general average of from 9 per cent. to 18 per cent. in all cases of perforated appendicitis, and from less than 1 per cent. to 18 per cent. in all types of the disease. Results as well as statistics will be influenced by many circumstances. Ideal hospitals, flawless surgery, and dependable surgical judgment may not be the boon of even a majority of the operated cases, but even with every favorable facility in hospital care and surgical technic we have failed with few exceptions, to reduce the mortality of this disease which is so simple in origin, so persistent in its warning and so fatal in the face of neglect.

The cause of our failure has long been known. John B. Deaver spent a part of every work-day denouncing delay in diagnosis and treatment of appendicitis as a pertinent factor in high mortality.

Throughout the last thirty years most surgeons of note, many of whose names grace the roll of this Association, have urged early diagnosis and

prompt operation in all acute attacks. Delayed diagnosis may become a fatal professional error. A clinically acute abdomen may not always present "classical symptoms," nor can the human individual be standardized as to his susceptibility to disease, nor as to his protective power in the presence of infection. Acute appendicitis may inflict greater damage and danger in ten hours upon one individual than in thirty hours upon another. There is no definite "period of safety" in any acute attack of appendicitis, nor is there any unerring index that marks the true course of the disease. All attacks, mild or severe, are tentative contributors to the disgraceful mortality rate which we view with a sense of professional shame.

John Bower[6] surveyed twenty-seven hospitals comprising all grades; he reviewed 6,123 cases with a resulting range in mortality from 1.64 per cent. to 11.29 per cent. Obviously, the fatality rate was lower in carefully supervised hospitals with highly trained physicians in attendance. The average lapse of time between initial symptoms and hospital admittance was 61.17 hours. The mortality rate ranged from 2.55 per cent. for those in hospital within twenty-four hours to 11.83 per cent. for those after seventy-two hours or three days. One out of every eighteen admitted to a modern city hospital is marked for death; over 80 per cent. of those who die perish from peritonitis, and finally, that of all who were hospitalized and operated within twelve hours of the initial attack, 99 per cent. recovered.

In one hundred cases of ruptured appendicitis with peritonitis operated upon by the writer, showing a range of age incidence from two to eighty-two years, the average duration of the disease before hospitalization was 5.4 days. Sixty-six had suffered previous attacks; nine of the twelve who died were from this group. Over two-thirds of the 100 cases had been given "home treatment" with laxatives, food, and sedatives, without medical aid. It is unnecessary to direct your attention to the truth that over 99 per cent. of the fatal cases are of those who have been home treated, or mistreated, for from three to six days before hospitalization. Such death-dealing action on the part of the family is not attributable to indifference or intentional neglect, but to ignorance of the actual menace of the disease. To this may be added an inherited fear of hospitals, and of the doctor who believes in operating. Economic conditions often enforce delay. Newspapers, although totally uninformed as to the circumstances, complications, or physical state of the subject, are prone to feature in broad headlines all deaths that occur following operation, in such a manner that the laity condemns the operation, not the delay and the faltering vitality, for the failure. Because of the fear thus engendered, surgery is to them the last resort and is strenuously avoided. From the present viewpoint of a layman we would draw the same conclusions.

Throughout the fifty years that appendicitis has been an acknowledged surgical affection, in our fervor to perfect our abdominal technic, we have given too little heed to the pre-operative period of the disease. It is this variable period of home treatment that renders so difficult the best efforts of the surgeon. It cannot be denied that the recovery rate in cases operated upon

at any stage of the attack depends largely upon surgical judgment and errorless technic, and that the surgeon, in knowing when to operate, what to do and what not to do with the late case, will rate a lower mortality.

In the present day, surgeons are plentiful and convenient; many of them are excellent, many striving to be, many content to remain as of yesterday, but most of them thoroughly capable of safely removing an uncomplicated six- to twelve-hour appendix. Therein lies one thought I wish to emphasize. If we earnestly desire to reduce our mortality in appendicitis to the minimum, the operation, if needed, must be performed before dangerous complications have developed. To accomplish this the diagnosis must be made early and carefully by a physician who is alive to the danger. That this may be realized, the doctor must be permitted to see the case during the period of comparative safety, within six to ten hours of the onset. When seen thus early, transportation to any distance necessary for satisfactory hospital and surgical service is practicable. This will not be accomplished without intensive lay instruction.

In 1879, fifty-three years ago, when Nicolas Senn[7] wrote "All cases of catarrhal and ulcerative appendicitis should be treated by laparotomy and excision of the appendix as soon as the lesion can be recognized," he was inviting early diagnosis and preventive surgery, our present theme.

Until the last few years public instruction in things medical was rather sharply limited to cancer, tuberculosis, diphtheria, smallpox and kindred diseases. True it is, that sporadically here and there arose a warning and admonition that we must recognize and operate early if we hoped to curb the death rate of appendicitis. The major part of our interest in the past has been centered on how best to conduct a case that has become critically ill. It is incumbent upon us to prevent the critical period.

The Journal of the American Medical Association and the American College of Surgeons long ago recognized the need of broad intensive lay education. Hygeia has presented many valuable lay articles, but it has reached too few families to reap the benefit the gesture merits. The radio has very likely been the most effective medium of broad dissemination, and occasional broadcasts from local medical societies or major medical conventions have created increased public interest. Insurance companies of high standing have made a more direct appeal to the reading public through paid advertising; their effort to conserve life and health deserves admiration and commendation. No motive may be fairly termed ulterior when its objective is preservation of life. There are still many simple and effective avenues of approach in lay education and many valid reasons why they should be utilized. The situation demands that each family be taught the potential danger of persistent abdominal pain and that they must promptly place the responsibility of the diagnosis and treatment upon their physician.

It will not be necessary to *force* this knowledge upon the public. The educational newspaper articles written by Doctor Fishbein on various health subjects have attracted wide attention. Not less than five such articles have dealt with appendicitis. He writes: "I am convinced that education of the

public is probably our greatest hope in controlling increased mortality from appendicitis."

Olin West, Secretary of the American Medical Association, informs me that the publication of articles on appendicitis in Hygea, and elsewhere, although reaching a very limited part of our public, has brought thousands of inquiries from its readers. He also states that this contact with the public on things medical constitutes an important part of the association's work; that one department alone answers from six to ten thousand inquiries a year from laymen, while thousands of others are answered in other departments. The thinking public is eager for a better knowledge of how to care for themselves and their children. From a humanitarian as well as an economic angle, with but few exceptions, they will welcome every aid toward preservation of life and health.

Ten years ago, before the Southern Surgical Association, the writer[8] presented a paper on "Errors in the Home Treatment of Appendicitis." A very definite period of home treatment invariably intervenes between the onset of disease and the physician's entry. It was my contention then, as now, that the high mortality rate in appendicitis is largely determined by the conduct of the attack before the doctor is called. Unfortunately, there are still a few doctors who will prescribe for colic by telephone, or send a sedative, or order a purge, or procrastinate in diagnosis, just as there are also many citizens who decry doctors and drugs until the fatal issue is apparent even to them; but a standard of action cannot be predicated upon the exceptions to the rule. An understanding public will welcome frank discussion of subjects inimical to their health and happiness. The physician, called early, will have sufficient time to work out a careful diagnosis, and, if necessary, to safely hospitalize the patient, and the surgeon will welcome the opportunity to forestall a peritonitis and the disastrous sequelæ that often follow. The economic saving to a community, in life and morbidity alone, will well compensate the efforts of all who participate.

Each year, the College of Surgeons holds community health meetings at all sectional and national conventions; public halls have been unable to accommodate the attendance. Radio talks on nation-wide hook-ups are given. Trained speakers cover senior high schools, junior colleges, community service clubs, and women's organizations on appendicitis, cancer and other diseases where fore-knowledge is of value. The public is ready to receive, the profession should be willing to give.

Our recognition of this challenge has been deplorably slow. John B. Murphy, that dynamic teacher and clinician, who more than any other of his period urged the substitution of prompt surgery for watchful waiting in acute appendicitis, said: "I desire to urge upon you, first, that you operate upon all frank cases; second, that you operate early to save yourself the humiliation of performing an ante-mortem operation." Our mortality, despite the medical and surgical progress, within the last fifty years has increased, and the

train of crippling sequelæ in those who survive a vicious attack constitutes an additional serious problem.

It was not my desire to include in this paper any dicussion of the operative or post-operative stages of appendicitis, although the supervision of both periods of the disease is of most vital influence in controlling mortality. It is tenable to assume that surgical judgment must be fitted to each individual case; that standardization of surgical treatment is unwise; that the present knowledge of sound technic and after-care will probably admit of but minor improvement as time goes on, and that primarily our hope must lie in an attack upon the true source of the high mortality, the first stage of the disease, and secondarily upon the general adoption of the most effective surgical technic in the neglected case.

Mature judgment during the operative stage is invaluable; neither radicalism nor timidity will best serve routinely. An active peritonitis demands a higher degree of mental balance than technical skill. In the opinion of Deaver,[9] precipitate or too radical removal during peritonitis and failure to insist on removal of the interval appendix are factors of great importance.

Charles Mayo[10] criticizes the tendency toward "radicalism during the danger stage and delayed or mistaken diagnosis."

Le Grand Guerry,[11] in reporting an enviable record of recoveries in acute diffuse peritonitis, selected his time and method of operation with extreme caution, dealing with each case on its own merits, with the most encouraging results yet reported.

The complications that so generously affect the mortality rate are numerous; peritonitis, ileus, residual abscess, and pylephlebitis probably lead the field. Post-operative hernia, obstruction from adhesions, thrombosis, embolism and intestinal fistulæ, exact a definite toll and increased morbidity. Lay education will undoubtedly reduce in quantity a most interesting phase of our surgical activity, as well as allay many of our most serious operative and post-operative worries.

Of the 500,000 cases of appendicitis reported in the United States in 1925, it may be definitely assumed that of the 25,000 who died more than 20,000 might have been saved had the victims had the services of an intelligent physician within the first six hours of the attack. This can be made possible only by a systematic, intelligently supervised program of lay education. It is natural that exception be taken to the dearth of scientific interest in this paper, and for that omission I most humbly apologize, yet my conception of the duty of a surgeon encompasses a broader and more humane field than may be sheltered under the banners of science and art. None is more anxious to save the lives of thousands of our citizens than the surgeon, even though the method entail no more thrilling nor heroic act than the substitution of a preventive early operation, with a negligible mortality, for a late and often incomplete one, with its high death rate and long trail of menacing after-effects. We have known for years that many lives would be saved by early operation. We have felt and known that ignorance of the danger caused

the delay, and that education alone would dispel that ignorance. We have probably felt that our dignity might be best conserved if we maintain an inherited scientific restraint and permit the family doctor to spread the protective gospel.

Preventive surgery is scientific progression, and is as truly essential as preventive medicine. In my humble opinion it should be accepted as a privilege as well as a scientific duty to join hands, by commission or otherwise, as suggested by Willis, with other medico-surgical and civic bodies to work out a plan whereby a dignified, intensive, self-accelerating program of general education upon the danger signs of this and other highly fatal diseases may be instituted. We would go to any extreme of effort to reduce the mortality of cancer were we privileged to do so. The dissipation of high mortality in appendicitis is equally important to the public welfare and far more promising of immediate results. Any preventable scourge that claims a citizen of the United States every twenty-five minutes of each day merits any effort or method to subdue it.

Thoughtful consideration is being given in various communities to the most simple, practical and effective method of presenting gratuitous advice to the public. In a certain community in Pennsylvania the profession has repeatedly broadcast by radio the common error of delaying the call for the doctor in the presence of persistent abdominal pain. A program is in effect that will insure information to every family.

Royster,[12] who has repeatedly reminded us of the potential danger of the pre-medical period, suggests unified action by local medical societies, health boards, civic organizations, schools, public health nurses, druggists, *etc.;* in others words, utilization of all existing groups that are already actively functioning and interested in public service. Now and then we find to our discomfiture that a doctor has been in attendance and has failed, through various reasons, to note the progress until too late for safe operation, or has mistaken the ailment for one of the many that, in the early period, may simulate appendicitis. Our medical schools and medical journals can reduce these errors to the minimum by reminding the physician that frequent inspection in suspected appendicitis is far less expensive than prolonged care after rupture has swept away the possibility of safe and prompt recovery. Doctor and laymen alike must know that the peristaltic urge of castor oil and its fellow assassins, given by loving relatives in forgivable ignorance, drives many mild attacks into fulminating activity.

If the combined medical and surgical profession will thus sanction and supervise an earnest effort to control the death rate in acute appendicitis, within five years a reduction to an insignificant rate will have been achieved, without stigmatizing our surgical pride or lowering the standard of our professional service.

In closing permit me to read an impressive admonition from the pen of a layman written eighty-six years ago: "The human race is afflicted with disease. Mankind as a body are sick and need a physician. They need effectual atten-

tion, and permanent restitution to health, energy and happiness. The race, then, must be educated. The rudiments of this education must consist in each one knowing himself in every essential anatomical and physiological particular, and then the world will not be cursed with ignorance, vice, disease and misery. Then physicians will be useful and beneficial, for their time and talents will be concentrated in the great work of social and moral reform, and their interests will not only consist in the amount of health enjoyed, but in the destruction of ignorance, violation and local wretchedness."

SUMMARY

The mortality rate in acute appendicitis has increased during the last two decades.

Medical and surgical care has vastly improved during this period without corresponding reduction in mortality.

There is less than 1 per cent. mortality among those operated upon within the first twelve hours of the attack. The average length of time consumed in nefarious home treatment without medical aid is from sixty to eighty hours. The mortality rate among those whose hospitalization has been delayed beyond thirty-six hours is 11 per cent., to 18 per cent., presenting a difference of from 10 per cent. to 17 per cent. as a result of unnecessary delay. Peritonitis is the cause of death in over eighty per cent. of the fatal cases. Operative care and surgical judgment are of extreme importance in the neglected case. Aside from this, the actual cause of death in acute appendicitis is public ignorance or disregard of the potential danger of abdominal pain, and unintentional mal-treatment before the physician is consulted.

Preventive surgery is operation of frankly surgical conditions before a critical state has developed.

Appendicitis is a surgical disease. It is the surgeon's duty to reduce the death rate wherever and however possible. In appendicitis, this reduction may be attained only by cautious operative technic and well-planned, intelligently directed lay education, which should be promptly instituted and promoted by all groups interested in public welfare.

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TREATMENT OF APPENDICITIS COMPLICATED BY PERITONITIS

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Since Fitz established the real nature of appendicitis in 1886, many hundreds of papers have been written on the subject and more operations for appendicitis have been done than for any other malady. It would seem, therefore, that the entire subject should be exhausted, the mortality lowered year by year and the operative treatment of the disease and its complications standardized. This is far from the truth, however. Appendicitis and its complications are still subjects of controversy, there is much difference of opinion and practice, and the death rate is on the increase.

The mortality of appendicitis is a subject about which there is deservedly a great deal of thought and discussion. Clean appendectomies have an almost negligible death rate. When the peritoneum becomes infected the mortality in different reports varies between 10 per cent. and 22 per cent. Here is a sharp and fatal difference in mortality and a number of writers have raised the question as to just how much drainage material actually aids in draining the peritoneal cavity and to what extent intestinal obstruction, caused by drains, contributes to the death rate.

These cases of peritonitis complicating appendicitis might be divided into three groups: First, early peritonitis, where the exudate is chiefly liquid and may be scanty or abundant, localized, spreading or diffuse; where the gut is injected and somewhat œdematous, but where the surface of the intestine is still smooth and for the most part shiny. Second, late diffuse peritonitis with the coils of the intestine everywhere adherent, with many small pockets of pus scattered widely and the intestine red and dull. Many of these patients die no matter what is done. Third, walled-off infected areas, secondary to acute appendicitis, where the patient comes in the hospital with a palpable mass, and, if operated on cautiously, and if the drains are confined to the walled-off area, give a good outlook as to life.

Sworn and Fitzgibbon[1] reported recently on appendectomies in St. Thomas' Hospital, London, over a ten-year period, 1920–1929 inclusive. There were 2,126 cases in which there were 231 cases of diffuse peritonitis divided into one-, two-, three- or four-day cases, with a death rate of about 19 per cent. In 487 patients with a palpable mass there were only seventeen deaths, a death rate less than 4 per cent. In the 1,340 patients without peritonitis the mortality was 1.71 per cent. From these figures and from many others that could be collected it is appallingly evident that peritonitis, as a complication of appendicitis, is a death-dealing malady.

In one group death is due directly to peritonitis and its contributing fac-

tors—paralytic ileus, dehydration, exhaustion, toxæmia and disturbance of the acid-base balance. In another group, death is caused by some complication—empyæma, pneumonia, infarction, septicæmia, *etc.*; and, in a third group, mechanical obstruction is the cause of death.

Cutting[2] recently said: "Post-operative ileus is due in almost all cases either directly or indirectly to peritonitis; about one-half of all cases of ileus are post-operative, and the condition of appendicitis accounts for by far the greatest number of cases of post-operative intestinal obstruction."

Just how many of the deaths following operations for appendicitis complicated by peritonitis are due to mechanical ileus it is impossible to say; certainly, a considerable number. When one considers that the average death rate for intestinal obstruction, exclusive of strangulated hernia, is about 50 per cent., this complication becomes a matter of grave concern.

We have been working, therefore, under the twofold risk of a spreading fatal peritonitis if we do not drain, on the one hand, and early or late mechanical ileus or disabling adhesions, following drainage, on the other.

When any operation is performed on tissues covered by the peritoneum this membrane insures a prompt sealing of the approximated wound edges. This is the keystone of abdominal surgery. But, this same beneficent and amazingly effective tissue, in the presence of drainage or infection, causes widespread adhesions which may lead to early or late intestinal obstruction.

Drainage is looked upon as a necessary evil. Every surgeon avoids it when he can and is fully alive to its risks and disadvantages. Its use is followed by many possibilities of mishap and misadventure—obstruction, paralytic ileus, adhesions, post-operative hernia, prolonged convalescence and fistulæ. There is scarcely a more disturbing time for patient and surgeon than the period following the placing of drains in the lower abdomen, especially if the patient develops distension, pain, vomiting and constipation. It is most difficult to know whether these symptoms are caused by paralytic ileus or by mechanical obstruction. To operate for paralytic ileus is to still further insult intestines already on a strike, and to fail to operate for mechanical obstruction is to deprive the patient of his chance of life. There is abundant experimental evidence that drainage material placed in the free peritoneal cavity does not drain the peritoneum. It becomes sealed off in a short time and acts only as an irritant around which omentum, mesentery and coils of intestine become adherent. In 1905, Yates[3] showed the futility of trying to drain the peritoneal cavity by means of cigarette drains or tubes made of gauze. In every instance the drains were promptly shut off.

Poynter,[4] in 1929, reported the experimental work of his department on peritoneal absorption and his findings were clear-cut as to the "reaction of the peritoneum to solutions and suspensions of particulate matter, to find out how absorption occurred and the paths taken." Bacteria and particles of matter found their way rapidly through the lymphatics in the diaphragm and entered the parasternal and paravertebral lymph-vessels. The process is rapid, beginning in three to five minutes. The only other channel of absorption dem-

onstrated was through the omentum. These methods of absorption were the same whether the peritoneum was normal at the time of injection or already inflamed.

Still more striking evidence of the ability of the peritoneum to care for itself when the cause of infection is removed, and of the ill-effect of peritoneal drainage in diffuse peritonitis was uncovered by Buchbinder, Droegemueller and Heilman,[5] in 1931. They operated on thirty-one animals and left an open tube of gut attached to the mesentery, and restored the continuity of the gut above and below the open section by an end-to-end anastomosis; 90 per cent. of these animals died of peritonitis. They then operated on thirty-three animals, following the same procedure, and at the end of twenty-four hours excised the open section of gut in order to remove it as a further source of infection; fourteen of these animals recovered. They then operated on another twenty animals and performed the same two steps described above, except that they left two abdominal drains in each animal, one down toward the pelvis and the other in the upper abdomen. Two were lost during operation. The other eighteen all died on an average at the end of four days; seventeen died of peritonitis and the eighteenth dog of peritonitis and pneumonia.

Just what happens when a moderate amount of blood is left in the peritoneum is not certain. It has been generally supposed that blood and bacteria in the peritoneal cavity create conditions almost ideal for the development of peritonitis. Most of us have always drained the infected peritoneum if a reasonably dry field could not be obtained. Allen showed that infected blood injected into the pleura of rabbits produced empyæma in a large percentage of them. In spite of the above belief of surgeons and the experience of Allen, Sparks and David[6] were unable to produce peritonitis in either dogs, rabbits or guinea-pigs, when autogenous blood mixed with broth suspensions of bacteria was injected into the peritoneal cavity.

There are a number of papers in which the authors take a decided stand in favor of closure of the abdomen in the presence of early spreading or diffuse peritonitis complicating appendicitis.

H. C. Miller[7] covered the subject very fully in 1930. He reviewed the literature, discussed the likelihood of drainage causing obstruction, and stressed the experimental evidence going to show how little actual drainage was done by drains in diffuse peritonitis, and concluded that drainage increases post-operative discomfort, prolongs convalescence and is a big factor in leading to secondary operations.

E. P. Hall, Sr.,[8] does not use drains for free pus in the peritoneal cavity and is confident that his mortality and morbidity rates have decreased. He drains all walled-in abscesses.

R. D. Kirk, Jr.,[9] thinks that the less drainage the better, and is confident that many bad results follow the introduction of drains among coils of intestines.

Stanley Raw[10] advocates closing the abdomen in all cases where the appendix has been removed. He has followed this method since 1921 and says there is less suppuration without drainage than with it.

B. Banks[11] leans strongly to non-drainage in all spreading and diffuse peritonitis whenever it is possible to remove the cause.

MARCHINI[12] reported 301 cases of localized peritonitis; 184 were drained with nine deaths; 117 were not drained with two deaths. There were 142 cases of diffuse peritonitis; 101 were drained with thirty-one deaths; forty-one not drained with seven deaths. When these figures are consolidated, 158 patients with localized or diffuse peritonitis were not drained with nine deaths, a little less than 6 per cent. motality; while 285 were drained with forty deaths, a fraction more than 14 per cent. mortality. We do not know how many of these forty deaths were caused by obstruction.

SWORN'S AND FITZGIBBON'S report is not so favorable to closure without drainage. Of 231 cases of diffuse peritonitis, 120 were not drained with twenty-one deaths, while 106 were drained with twenty-three deaths, the mortality in each group being about the same.

In 1921, ANDREW,[13] of the Victoria Infirmary, Glasgow, closed seven cases of peritonitis without drainage after removing the appendix and making a clean toilet of the infected peritoneum, and leaving iodoform emulsion in this portion of the peritoneal cavity. They were also given *Bacillus coli* vaccine after operation; all recovered. There was some infection in the wound in three cases.

The reports from hospital laboratories as to the bacterial content of the exudate found in the peritoneum are often disappointing. Even when there is every optical evidence of peritonitis it often happens that the laboratory reports no growth. If we could have a group like that led by Dr. Frank L. Meleney,[14] reports might show a more abundant and more varied peritoneal flora in peritonitis. Dr. Robert T. Morris, in discussing a paper by Dr. John E. Jennings, read before the New York Surgical Society, stated the entire matter with great accuracy. "Nowadays one who goes after any particular bacterium finds it by special methods."

Just putting some material from the peritoneal cavity into standard media and running it through the laboratory in ordinary routine will fail to recover many organisms that might be found. If the different organisms whose presence is either possible or likely were followed through by specially interested bacteriologists making use of special methods, the bacteriological findings would be more in keeping with the clinical appearance of the peritoneum at operation.

Until about two years ago I had been treating early peritonitis complicating appendicitis by drainage. These drains were introduced very much as we had been taught by the late Dr. Frank Martin. After removing the appendix through a McBurney incision two fingers of the left hand were introduced into the pelvis along the bladder wall, pushing the intestines back, and a small rubber tube and one small cigarette drain were introduced into the pelvis until the ends rested in the bottom of the peritoneal pouch in front of the rectum. Another cigarette or small rubber tube was placed lateral to the ascending colon with the end resting in the subhepatic space. The McBurney incision was closed snugly around these drains, and most of the patients made a prompt and satisfactory convalescence.

But there were a certain number who came to grief and in almost every instance intestinal obstruction was the complication present. Even when this condition did not actually exist there was often a period of uncertainty because of the presence of paralytic ileus or incomplete obstruction due to an-

gulation. In the spring of 1930, within a few weeks, four patients on whom I had operated for peritonitis following appendicitis and drained, developed mechanical obstruction and two of them died. At operation all four were completely obstructed by angulation of a loop of small intestines in the drain tract. The remainder of the peritoneum was free of adhesions or any evidence of infection. The possibility of intestinal obstruction following low abdominal drainage has always kept us anxious and apprehensive, especially if the drains were placed adjacent to coils of free intestine.

To close the abdomen, however, in the presence of peritonitis seemed a foolhardy thing to do, but less and less drainage was being used after pelvic inflammatory disease, intestinal suturing and cholecystectomies, and, being harassed by the imminence of obstruction, we began to close the abdomen after appendectomy where early peritonitis was present. At first we closed the seropurulent cases only, but as these patients did well, we gradually extended the list to include all cases of early peritonitis whether the appendix was thrombotic, gangrenous or perforated, and irrespective of the amount of fluid present or the extent of the involvement of the peritoneum.

This report is based on patients admitted to my service in the University Hospital, Baltimore, since June, 1930. Most of these patients were operated on by myself, although some of the operating was done by Dr. Hugh A. Bailey, who is the joint author of this paper and was resident surgeon last year, and Dr. George H. Yeager, who is the resident surgeon this year. Altogether, 251 patients have been operated on for appendicitis since this date, a period just short of two years. Of this number, seventy-two were chronic and 179 were acute. Of this latter number 113 patients were without any peritoneal involvement and were operated on in the usual manner. Eleven patients had late diffuse peritonitis and were drained. Four of these died; two of these four were reoperated on for intestinal obstruction. Seven came in with a mass and were drained with no deaths. There were forty-eight patients during this period with early peritonitis either local, spreading or diffuse. All of these abdomens would have been drained if we had been following our original methods. This group was closed without drainage following an operative technic to be presently described. There were seventeen positive cultures, fourteen of which were the colon bacillus.

There was no death in this group and no serious complication. There was no case that required a second opening of the abdomen for any cause and no extensive infection in the abdominal wall, although, as stated elsewhere, in a number of instances the abdominal wall was drained. There was a striking lessening in the severity and duration of paralytic ileus in these cases, and the convalescence was much shorter.

We have followed a definite technic in operating on these patients. We nearly always use the McBurney approach modified by a short transverse incision in the anterior sheath of the rectus muscle. This gives more room and an easier approach to an adherent or abnormally placed appendix. If the appendix is found thrombotic, gangrenous, or perforated, the wound edges are

protected by gauze. The peritoneum will take care of the infection much better than the structures of the abdominal wall. If the cæcum is mobile it is gently rolled out and the base of the appendix brought into view. Depending upon the mobility of the cæcum, and the length, position and fixation of the appendix to surrounding structures, this maneuver may be easy, difficult or impossible.

Whatever the condition found, an unhurried and painstaking attempt is made to free the appendix and clamp and cut its mesentery. Care is taken to handle the appendix with the fingers as little as possible. As soon as it is free, it is wrapped in gauze, delivered as well as possible, and removed. A careful closure and turning in of the stump follows. A very careful ligation of the mesenteric vessels is carried out. Raw surfaces are covered. This suturing is all done with fine silk, except the ligature on the appendix, which is catgut. The abdominal cavity is everywhere emptied of liquid exudate with the sucker. Most of the purulent matter is found in the pelvis and right iliac fossa. Very little packing is used; narrow retractors and spatulæ are used to get exposure. After the peritoneal cavity seems free of exudate, the appendix region and pelvis are exposed by using the fingers to push back the cæcum and small intestine, and warm normal salt is poured into this area slowly while the sucker pumps it out. If there are a number of small masses of coagulated fibrin adherent to coils of intestine, these are gently removed with moist gauze or smooth forceps. The peritoneum is then carefully closed, as a smooth peritoneum is the best guarantee against postoperative adhesions.

At this stage the towels are changed and the used instruments discarded, the gauze protecting the wound edges removed, the gloves changed, and the raw surfaces wiped over with alcohol, and, if much fat is present, with ether also, and the abdomen closed layer by layer. If the peritonitis has been extensive, with considerable coagulated exudate, and the appendix difficult of removal, a small tube drain is left through the fat down to the aponeurosis of the external oblique muscle.

We are anxious to be understood that all of these patients had acute appendicitis with early peritonitis. Sometimes the peritonitis was not suspected until the peritoneum was opened. They were not victims of longstanding infection. While the pulse rate was often rapid and the temperature and leucocyte count elevated, they were not dehydrated by vomiting and starvation but were, in the main, in good condition. When the abdomen was opened, although peritonitis was present and the intestines were injected and often somewhat dull and œdematous, they were not much distended or paralyzed, and there was no pocketing or walling-off. In a number of cases small patches of coagulated exudate were removed from intestines that had been in contact with the appendix, but in no case was this condition widespread.

Not all cases of suppurative peritonitis complicating appendicitis were

closed without drainage. There were a number of conditions in which drains were used. A considerable group of neglected cases of appendicitis came in with a palpable mass indicating usually a walled-off suppuration. These were drained and the rest of the peritoneum disturbed as little as possible. Sometimes in these cases it seemed wise not to look for the appendix unless it came readily into view. If the cæcum, after the removal of the appendix, could not be securely closed, a drain was left in. Sometimes the closure of the appendix stump was rendered more secure by suturing over it a bit of fat from the mesentery. If bleeding from the thickened, œdematous or short mesentery could not be entirely controlled, a small drain was left down to this area.

The most hopeless group were patients with late diffuse peritonitis, with adherent coils of intestines, walling-off many small pockets of pus, with the gut dull, red and distended, and covered here and there with masses of coagulated exudate. These patients presented the symptoms and signs of advanced peritonitis—a stiff, board-like abdomen, rapid pulse, drawn and anxious features, dehydration and disturbance in the acid-base balance. These were drained.

The important things in early peritonitis are not the kind and number of organisms in the peritoneum or the amount or extent of the exudate, but the source of infection, and whether or not the avenue through which the organisms are reaching the peritoneum may be promptly gotten at and closed. If this can be accomplished in the early stages of peritonitis, drainage need not be so widely used as has been practiced.

When the Fowler position came into vogue most surgeons used only dependent drainage and lessened the bulk of drainage material used. As the years passed it was observed that the long-continued Fowler position was associated with an increase in post-operative phlebitis and pulmonary embolism, and many surgeons were of the opinion that the jack-knife position predisposed to stasis of the venous circulation in the pelvis.

It is our belief that the improvement brought about by the Fowler position and dependent drainage was due in part to the simpler operation, relative absence of trauma, and the smaller and fewer drains, rather than to either the upright position or dependent drainage.

CONCLUSIONS

(1) Exclusive of strangulated hernia, peritonitis is the chief cause of intestinal obstruction.

(2) In the majority of instances, it is not the peritonitis *per se* that causes the adhesions and bands leading to obstruction, but the reaction of the peritoneum to the drains.

(3) Drainage material, especially in the lower abdomen, often causes widespread adhesions between loops of intestines, mesentery, omentum, pelvic organs and abdominal wall.

(4) Drains are soon sealed off and do not drain any considerable portion of the peritoneum.

(5) Paralytic ileus seriously obscures the clinical picture when drains are left in the abdomen.

(6) Pelvic drains increase the incidence of post-operative retention of urine.

(7) Drained abdomens are more likely to develop troublesome, painful, or disabling late post-operative adhesions.

(8) Late intestinal obstruction is more likely to occur in drained than in undrained abdomens.

(9) None of these considerations should carry any weight if the risk to life is increased by closure without drainage.

(10) Evidence is accumulating that the introduction of drains into the abdomen in the treatment of early peritonitis may be dispensed with, without increase in the death rate.

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DISCUSSION.—DR. HUBERT A. ROYSTER (Raleigh, N. C.) said that for one who has spent many years and hard labor in the study of appendicitis and now feels that he knows less about it than ever, it is refreshing to see this subject on the program. In his belief it is not beneath the dignity of this Association to talk about appendicitis. In 1905, John B. Murphy shouted in one of his explosive efforts: "Is it time to stop talking about appendicitis? No, it is just the time to begin talking about it and talk about it most seriously and emphatically." That challenge is just as alive today as it was twenty-seven years ago.

Doctor Royster was afraid that as surgical teachers and operators this matter has been relegated to the pigeon-hole of solved problems while attention is being paid to what is regarded as more interesting and more modern matters. If one understands the pathology of appendicitis, one can solve most of the other problems. The whole question appears to centre around just this statement: That appendicitis is a going concern, a continuing process, and that the attack is not the disease but only the knock at the door, saying, "Let me out," and further, that every acute appendicitis attack, so-called, is a case in which there has been not only previous pathology but previous clinical symptoms which perhaps have not been recognized.

Doctor Royster was a disciple of Aschoff on this point: Whether one considers there is such a thing as chronic appendicitis or not, there has been chronic or continuing distress in the appendix before the so-called cardinal symptoms of the acute attacks are present, and in most diseases cardinal symptoms are merely terminal events.

Appendicitis obliterans, he believed, was first spoken of by Nicholas Senn, and whether one regards it as a physiological or pathological process, it is a question to determine whether the strictures produced off and on by the obliterating type of the disease, showing spaces between them, or becoming perfectly solid, are part and process of the real pathology which is in most cases in the wall of the appendix, and not in its lumen originally.

On the physiological side it might be explained somewhat by the work of Adami, who suggested that the appendix had a function which was to act as a hydrostatic propeller to throw the contents of the cæcum upward, and he called attention to the very marked peristaltic action in the appendix. A six-inch appendix removed immediately and placed on a glass table will within fifteen minutes contract about two inches of itself and when pulled out, will come to its original length.

If one considers that it has that action in the constant contraction and relaxation of the appendix in propelling the contents of the cæcum upward, it will so produce a chronic type of inflammation in its wall. In nearly all of these cases there are associated rings on the mucosa, which are very much like the rings in a tree, showing the number of attacks which the patient has had previously.

DR. EUGENE H. POOL (New York City) remarked that Doctor Shipley's paper suggested one or two things especially in regard to drainage. All accept the fact that the wound should be closed without drainage if it is reasonable; but a certain number of cases, as he says, must be drained. Now a word about the nature of the drains, but first in regard to the aspirator. Doctor Shipley makes a great mistake in irrigating within the peritoneal cavity. Blake advocated irrigation many years ago but he has since admitted the fact that it is a mistake.

Taking the nature of the drains in the cases where something must be introduced, Shipley referred to using a rubber tube down into the pelvis. Years ago it became evident that any kind of solid drain produces pressure necrosis, and is a very poor form of drain.

Many years ago when the speaker was house surgeon, and there were a large proportion of advanced and neglected cases of appendicitis to deal with, the incidence of fecal fistulæ was extremely high. It was suggested that perhaps the use of the

rubber tubes which was the custom favored these fistulæ. Soft rubber tissue drains were substituted with very marked reduction in the occurrence of fecal fistulæ.

In regard to soft rubber drains, they have found it advisable to introduce the so-called cigarette drain to the site which is to be drained. Recognizing that this in itself will not drain for long they therefore introduce another to the neighborhood of the site. The peritoneum is closed up to the drains to prevent omentum or intestine projecting along the side of the first drain. The second drain is removed in about thirty-six to forty-eight hours and it leaves a track along the side of the main drain or drains thus ensuring adequate drainage.

In badly infected cases only sufficient sutures are introduced to close the peritoneum beside the drains. The rest of the wound is left open; the reason for this is that when they did a partial suture above and below the drains in an appreciable number of cases there was found at the end of four or five days the typical colon infection and they had to open the wound, finding often sloughing of the aponeurosis of the external oblique. This is due to the tension of the sutures and the ready growth of the colon bacillus in the partially closed wound. When the wound is left open to the peritoneum there is no slough nor necrosis, as occurs with the colon infection. The wound rapidly granulates. No time is lost in convalescence and the incidence of incisional hernia is definitely diminished.

Dr. Leonard Freeman (Denver, Colorado) said that Doctor Horsley has called attention to obliterating appendicitis. Whether it is due to involution or to inflammation perhaps is not the important point. The important point is that a zone of inflammation is almost always present just in front of the obliterating portion of the appendix. The condition thus becomes a true chronic appendicitis manifesting itself constantly and indefinitely. The consequent symptoms may be due to several causes: to absorption by the blood-vessels; to inflammatory material; to the compression and irritation of the vegetative nerves and ganglia that Doctor Horsley has spoken of; or to lymphatic absorption.

Pribram, of Berlin, has called particular attention recently to lymphatic absorption and deserves our consideration. He speaks of the intricate ramification of lymphatics in the post-peritoneal area and how they connect up all the organs within the abdomen. When this network becomes infected, it may produce a great variety of symptoms in connection with these organs. The most obvious manifestation is enlargement of mesenteric lymph nodes, which in turn, may irritate the vegetative fibres still further, thus causing additional symptoms. Doctor Mayo has just called attention to this maze of lymphatic distribution within the abdomen.

It is not the acute form of appendicitis that causes this trouble; it is the chronic form. The acute form closes the lymphatics so that absorption does not occur into the post-peritoneal lymphatics; but the chronic form leads to absorption continuously over a great length of time, particularly the obliterating form, in which the disease may continue for months or even for years. When this lymphatic system is once involved the trouble does not always disappear when the appendix is removed. The same thing can be said of the gall-bladder, which is also a prominent port of entry into the lymphatic system as well as the appendix.

If this view is accepted it throws light on many symptoms, particularly those which often remain after the removal of the appendix. It also indicates that all chronic appendices, including the obliterating form, should, when encountered, be removed early and *completely*, because a small remaining stump may be the cause of persistent trouble.

Dr. Le Grand Guerry (Columbia, S. C.) remarked that there is one great underlying principle in handling suppurative cases of appendicitis and this principle can be more clearly understood if one considers the background upon which it rests.

His own experience may be tabulated as follows:

	No. Cases	No. Deaths	Mortality
(1) Recurrent appendicitis	1409	0	0
(2) Acute appendicitis	822	1	0.12%
(3) Gangrenous, ruptured, localized abscess	610	5	0.82%
(4) Gangrenous, ruptured, with diffuse peritonitis	93	10	10.75%
(5) Cases *in extremis*; drainage; appendix not removed	9	3	33.3%
(6) Appendix removed in course of other operations	396	1	0.25%
	3339	20	0.60%

In the first group there are 1,409 cases in which the interval operation was done for so-called recurrent attacks of appendicitis without mortality. There were no deaths in this series. The only mortality connected with this type of case is the mortality incident to some unforseen calamity. Occasionally a recurrent appendicitis in very stout people, in which the appendix is deeply placed and inaccessible, can be quite difficult.

In group two there were 822 cases with one death: a mortality of 0.12 per cent.

By the term acute is meant exactly what the word implies. This group includes all of the definite, unmistakably acute cases up to the point of perforation. Most of the appendices were the seat of definite gangrenous areas. No case was included in this group in which the appendix was actually the seat of perforation.

In group three there was gangrenous, ruptured appendix with localized abscess. In this group there were 610 cases with five deaths or 0.82 per cent. mortality. In a group of localized appendiceal abscesses of this size one would very nearly run the gamut of intraperitoneal suppuration.

In group four there was a gangrenous, or ruptured appendix with diffuse peritonitis; ninety-three cases with ten deaths or 10.75 per cent. mortality. The cases in this group were operated on immediately.

He would have occasion to refer to this group in his closing remarks for thereby hangs a tale.

In group five there were cases *in extremis*; drainage; appendix not removed; nine cases with three deaths or 33.3 per cent. mortality. He made a separate group of these nine cases for two reasons: First because they were well nigh moribund from long-continued suppuration, and secondly, they were the only cases in the entire series in which the appendix was not removed. The fact that the appendix was not removed may have had some relation to the mortality rate: on the other hand one could reason that the mortality might have been higher had the appendix been removed.

In group six there were 396 cases in which the appendix was removed in the course of other operations. This group is added to the study for the purpose of showing what relationship, if any, the removal of the appendix during the course of other operations has to the mortality rate. He had included in this group only the cases in which the appendix was unmistakably diseased: such an appendix as one would feel justified in removing were there no other operation necessary. It is not our practice now, nor has it ever been, to remove an appendix simply because we were in the abdomen and it could be done.

Taken out of the above résumé of cases is the following:

	No. Cases	No. Deaths	Mortality
(1) Gangrenous, ruptured, localized abscess	610	5	0.82%
(2) Acute, diffuse peritonitis	93	10	10.75%
(3) Acute, diffuse peritonitis, deferred operation	128	2	1.5%
	831	17	2.05%

There is one series of cases in this grouping to which especial attention is directed and the group is presented with that purpose in view, *viz.*, the series of 128 cases of acute diffuse peritonitis in which operation was deferred. On the handling of these cases the question of the mortality rate largely rests. The whole question of mortality naturally hinges on the cases seen for the first time on the third or fourth day of the attack, cases with acute spreading infection. He emphasized particularly the point that none of these patients was operated on immediately; they were treated as outlined by Ochsner. With two exceptions, all were safely operated on at a later date; and in each case a gangrenous or ruptured appendix, with pus, was demonstrated at operation.

Contrast ninety-three cases of acute diffuse peritonitis operated on at once with ten deaths, or a mortality of 10.75 per cent., with 128 cases of acute diffuse peritonitis in which operation was deferred, with two deaths or a mortality of 1.5 per cent. Occasionally the Ochsner method has been supplemented by a simple incision and drainage under local anæsthesia, to relieve absorption from pus under tension.

These 128 cases in the statistics are included in the group of 610 localized appendiceal abscesses; likewise the two deaths which occurred previous to operation are included in the five deaths in the same series. These cases have been separated for the purpose of illustrating the difference between the mortality when the cases of acute diffuse peritonitis were operated on immediately and when operation was deferred.

In conclusion no claim is set up that this is the only way, or even the best way, to handle these critically ill patients. He simply presented a consecutive series of operations extending over a period of thirty years and is concerned with 3,339 cases. He emphasized the point that this mortality rate has been sustained throughout the entire time.

The one primary point that he was interested in making is this: If the work outlined above means anything it means that to do a formal operation on a patient critically ill with a diffuse peritonitis from a perforated appendix is to invite disaster.

Dr. Philemon E. Truesdale (Fall River, Mass.) noted that the mortality in appendicitis among physicians is higher than in any other class of the population. In 1930, the mortality among doctors was twenty-five per 100,000, whereas among the general population it was eighteen.

In his own family, four children out of seven had been operated upon for appendicitis before the age of ten without incident. He believed that the twenty-five doctors who died in 1930 from this disease would be alive today if they had been operated upon in childhood, before they became so important and so enlightened that fear, conservatism, consultations, and business matters led the vast majority of them to procrastinate beyond the point of safety.

Unfortunately, in general, it seems necessary to appeal very strongly to the element of fear in order to get consent for early operation. Fear of death must first be instilled into the mind of the patient when he is seriously afflicted. Fear of the consequences of delay must be instilled into the minds of members of the family. Fear that delay will not pay in the long run must be instilled into the mind of the attending doctor. Finally, fear of postponing operation even for hours must be inculcated into the mind of the surgeon. He should be afraid of the consequences of too much surgery in cases where suppuration has occurred and the appendix is difficult to find.

Dr. Franz Torek confined his remarks to one phase of the subject, "Diffuse Suppurative Peritonitis." This caption includes only those cases in which the purulent serum extends well over to the left side as well as to the upper abdomen and the pelvis. If a free purulent peritonitis extends only over a limited space, to the mid-line or slightly beyond, it should be called "Spreading Peritonitis," and if a collection of pus, no matter how large, is walled-off from the remaining peritoneum, it is called "Circumscribed Peritonitis" or simply "Abscess." This distinction is necessary, because the treatment varies with the different forms. Doctor Torek has been interested in "diffuse suppurative peritonitis" since 1902 and published his first eighteen cases in the Medical Record, December 1, 1906, where each of the cases is described in detail.

All agree that in diffuse suppurative peritonitis the appendix and the pus must be removed and the peritoneum must not be damaged. To evaluate the mode of procedure, which differs in different hands, a consideration of the following observations may be of help. In a case that has lasted longer than a day or two, ample opening of the abdomen will, after the pus has run out, often reveal very fine fresh adhesions attaching one loop of intestine to another or to the parietal peritoneum. These are usually so fine that a mere touch will separate them and evacuate collections of pus which may be considerable in quantity and may be far distant from the appendix. Several such collections may be encountered in the same case. To any one who is familiar with this condition it must be evident that the Fowler posture cannot be effectual in causing the pus to gravitate into the pelvis and to flow out from there through a drain. Even before these fine adhesions have been established the pus will be prevented from running into the pelvis if the intestines are more or less distended. Likewise, the attempt at washing out the peritoneal cavity from a small appendix incision by the use of a long double-current metal tube, as recommended by Blake in 1904, will fail to accomplish its object, as only a small part of the peritoneal cavity will be washed in this way. These methods of procedure could be effectual only in very early cases.

Doctor Torek makes a median incision from pubis to two inches or more above the umbilicus. As the peritoneum is incised, the pus flows from both sides of the incision. In one case, a successful one, it spurted a foot high as the knife entered the peritoneum. The suction tube is used only under guidance of the eye, as any damage of the peritoneum by this instrument would lessen the chances of recovery. For the same reason the use of wipes, especially their energetic use, is to be discouraged. After the bulk of pus is eliminated, the appendix is quickly removed and the peritoneal cavity is thoroughly and systematically flushed with large amounts of saline poured from flasks. First the exposed intestines are rinsed, next the cæcum and right gutter, then the pelvis and finally the left gutter, until the water flows out clear. The hand assists the cleansing by gentle to-and-fro motions. When fresh adhesions are encountered, they are separated, as pus will usually be found behind them. The large incision makes it possible to handle the peritoneum very gently during the cleansing process. Eventration, of course, is avoided, if possible, but a comparatively short eventration will be less hurtful to the congested peritoneum than extensive and often ineffectual stuffing with gauze pads.

The abdomen is then closed without drainage. The omission of drainage is a very important step in the management of these cases. Doctor Shipley has shown the inefficiency of drainage. It is impossible to drain the peritoneal cavity, and any attempt to do so will interfere with the reparative power of the peritoneum. Only in a few cases where, at the root of the appendix, the cæcum appeared to be threatened with necrosis, a drain was introduced through a separate opening to take care of that restricted area.

The closure of the abdomen is done by through-and-through sutures, not only because the saving of time in these cases is important, but also because the abdominal incision is infected and a separation of the different layers would spread the infection.

In the after-treatment no attempt is made to move the bowels for about four days, as the inflamed peritoneum requires rest. At that time a small rectal irrigation is permissible, the administration of a regular enema being reserved for the fifth or sixth day.

Doctor Shipley has referred to the adhesions caused by the presence of the drains. In this connection the experience in one of Doctor Torek's cases is of interest. As the pain was most intense in the upper abdomen, the possibility of perforation of other organs had to be considered, and the incision turned out to be the longest in the series, from ensiform cartilage to pubis. Owing to enormous distention the gut had to be opened in three places to allow gas and fluid contents to escape. Sixteen months after the operation the patient returned to be operated for a large post-operative hernia, at which occasion the peritoneum was found almost entirely free from adhesions, a condition probably due largely to the omission of drainage.

Of these eighteen cases all that had been operated in the first seventy hours of their peritonitis were saved. One patient operated at the end of the third day and two operated on the fourth day died. Some cases operated on the fourth day recovered. Of the three that died, one was moribund when operated, another was so badly septic that the operation did not even temporarily halt the sepsis.

On December 5, 1908, Doctor Torek reported a second series of eighteen cases in the New York Medical Journal, in which the mortality was exactly the same, 16 2/3 per cent. The cases were not selected, operation being refused in only one case, that of a patient who was moribund and died unoperated upon a few hours after admission. Operations subsequent to these thirty-six cases had a lower mortality, but they have not been tabulated.

Dr. J. Shelton Horsley (Richmond, Va.) said that he was not for a moment advocating promiscuous appendectomies because of obliterative appendicitis. It is extremely difficult, if not almost impossible, to make even a probable diagnosis of obliterative appendicitis before the abdomen is opened. There may, however, be some cases in which this diagnosis may be suggested by the symptoms and physical signs which should be thoroughly studied.

Any one who carefully observes both grossly and microscopically the obliterated appendices he removes, can hardly make any other conclusion than that the diseased process is a chronic inflammatory one.

In regard to drainage, it is too often considered solely mechanical. It is partly that, but it is largely biological. In an appendicular abscess one puts the drain down into the abdomen for the pus to run up-hill, and expects the patient to get well. The patient usually does get well. But up-hill drainage with pus in the thigh or in the pleural cavity is usually not so successful, because in regions of this kind with a very poor lymphatic supply the drainage should be gravity drainage from the lowest point. The abdominal cavity is enormously supplied with lymphatics and with lymph. The drain one places in the abdomen causes a reaction that induces the lymphatics to pour out fluid toward the drain in an effort to expel the drain as a foreign body. In this way, the large amount of lymph that is diverted from the normal circulation and poured out along the drain tends to wash out the septic material.

CLOSING VERY LARGE HERNIAL OPENINGS

By William Edward Gallie, M.D.
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At the meeting of the American Surgical Association held in 1922 a method of treatment for large ventral and inguinal hernias was described which involved the repair of the opening with autogenous sutures made from fascia lata.

Experience with this method extending over a period of ten years has been quite satisfactory and there is no question that it has greatly reduced the incidence of recurrence and widened the field in which operation is indicated.

There are some cases, however, in which the hernial ring is so large that no method of suture can adequately close the opening. There are others in which, while it is possible to draw the edges of the opening together by tight lacing of the suture, this can be done only with such an increase of the intra-abdominal pressure as to seriously endanger the life of the patient. In our earlier cases we tried to overcome this difficulty by simply filling the opening with a filigree of fascial sutures, much as one would darn a sock. In most cases this has proved successful but unfortunately, in a certain number, recurrences have developed which subsequent operation has shown to be due to protrusion through chinks between the sutures. We have accordingly been on the lookout for a more certain method of closure.

This has been found in a combination of the patch transplant with the living suture. It will be remembered that the defect in the patch transplant was that it could not be depended upon to heal strongly into the opening. There was no doubt that it could be expected to live but there was great doubt in regard to the strength of the scar and areolar tissue that joined its edges to the hernial ring. This uncertainty can be overcome by using as a patch transplant a sheet of fascia lata whose ends have been split into quarter-inch strips so that it resembles the old-fashioned many-tailed abdominal bandage. When the strips have been threaded on needles they are passed through the thick margins of the ring and those of one side of the opening are tied to those of the other, bringing the edges as closely together as seems desirable. In this way a strong aponeurotic structure, free of chinks and other weak spots, is securely fastened into the defect and may be depended upon to close the opening permanently.

The method is particularly applicable to large ventral hernias and most frequently to hernias resulting from suppuration following operations on the gall-bladder and stomach. It is useful also in cases of large direct inguinal hernias, particularly those in which the abdominal wall is feeble and in which several unsuccessful operations had previously been performed.

In the case of the ventral hernias a few special points in technic should

be observed. In preparing the hernial opening for the closure no attempt is made to separate the various layers from one another as this definitely weakens the wall. The peritoneum is pushed back from the edge of the opening for half an inch or more so that the needle may be passed from within outward

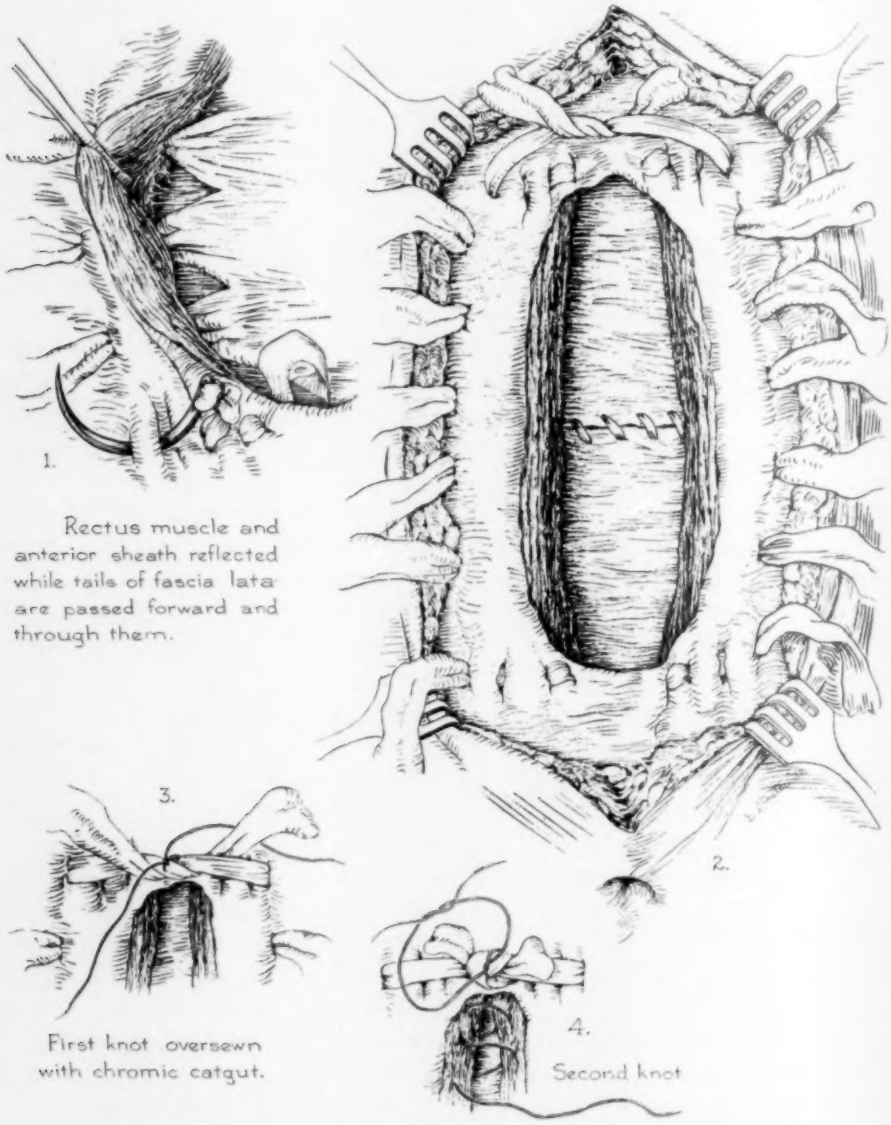

1.
Rectus muscle and anterior sheath reflected while tails of fascia lata are passed forward and through them.
2.
3.
First knot oversewn with chromic catgut.
4.
Second knot

DIAGRAM 1.—Wide ventral hernial opening closed by two sheets of fascia lata placed edge to edge. The inserts show the method of passing the tails through the edge of the hernia ring, and the method of tying and oversewing the tails.

through the edge of the ring without entering the abdominal cavity. If the hernial opening is longer than three and one-half inches it will be necessary to cut two patches from the fascia lata which will be laid side by side across the opening. As a rule, two patches of fascia, five inches by three and one-half inches, can be obtained from the lateral aspect of a single thigh. The

ends of the patches are then split into strips about one-quarter of an inch wide and by means of a fascia needle passed through the edges of the ring as shown in Diagram 1. If a second patch is needed it is laid edge to edge with the first and the two are sewn together with a fine strip of fascia lata threaded on a needle. At the ends of the opening, special precaution is taken to weave the tails into the edge of the ring so as to prevent a protrusion over the end of the fascial sheet. When all the tails have been drawn through the abdominal wall they are tied together, each to its fellow of the opposite side, and the edges of the opening drawn together as closely as seems safe. If they can be brought into contact without too much tension, so much the better, but, if they cannot, the surgeon may rest assured that the deep side of the defect in the abdominal wall has been permanently closed off. Often it is possible, where the deep portion of the opening cannot be drawn together, to close the anterior rectus sheath with catgut or a suture of fascia and this shuts off the sheets of fascia from view and seems to be an advantage. Care should be taken to oversew the knots in the tails of fascia with catgut as these have a strong tendency to slip and untie when strain is put upon them.

In inguinal hernia the need for the many-tailed fascial sheet is not great. Occasionally, however, cases appear in which the abdominal defect is very large or in which the abdominal muscles and Poupart's ligament seem too weak to withstand strain after any form of suture, and for such cases this method is useful.

The details of the operation are similar to those already described and are well illustrated in Diagram 2. The sheet of fascia which is obtained from the thigh is 2½ to 3 inches wide and 3½ to 4 inches long. Its two ends are split into quarter-inch tails which, by means of a fascia needle, are passed through the recurved edge of Poupart's ligament on one side and through the internal oblique muscle and its aponeurosis on the other. When the tails are pulled up tight the fascial sheet completely occupies the space in the posterior wall of the inguinal canal normally occupied by fascia transversalis and presents an impenetrable barrier to the protrusion of a hernia. Precaution should be taken to weave the lower tails into Gimbernat's ligament in such a way as to prevent all possibility of a protrusion around the lower end of the sheet and at the upper end of the canal the edge of the fascial sheet should be placed deep to the internal oblique muscle beyond its origin from Poupart's ligament so that a protrusion around the outer edge of the sheet would be impossible. As a rule the sheet should extend beyond the normal position of the internal ring so that the cord must be allowed to enter the abdomen between two adjacent tails. The tails are now drawn taut and tied together and the knots are oversewn with catgut as shown in the diagram. The external oblique is then closed in the ordinary way.

In each of the operations in which we have used sheets of fascia to close large hernial defects variations in technic have occurred according to the difficulties encountered. It is unlikely that any surgeon will ever find two cases alike so that anything like a standardized technic is impossible. If the general principle, however, is adopted of shutting off the opening on its deep

side with a strong sheet of fascia which is fixed into the borders of the defect by tails cut in the end of the sheet and if care is taken to weave the tails into the ends of the opening so that a protrusion cannot occur around the margin of the fascia, one may rest assured that the risk of recurrence will be small.

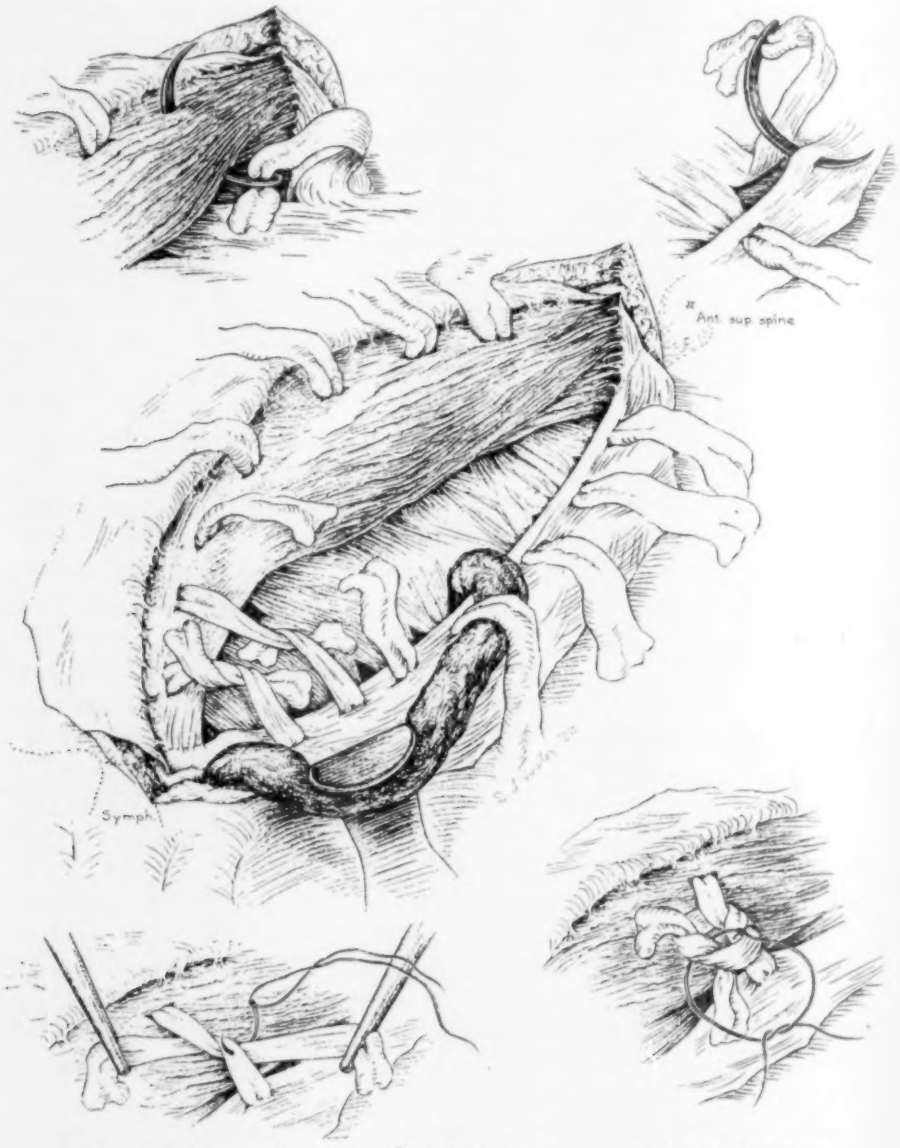


DIAGRAM 2.—Repair of posterior wall of inguinal canal by many-tailed fascial sheet.

The disability resulting from the removal of sheets of fascia from the thigh is fortunately very slight. Occasionally, patients complain of a slight sense of weakness, but as a rule they do not. Under any circumstances, the disability is negligible when considered in relation to the relief the patient has experienced in the closure of his hernia.

ABDOMINAL INCISIONS AND THEIR CLOSURE

By Arthur Dean Bevan, M.D.
of Chicago, Ill.

One of the most important subjects in abdominal surgery is that of abdominal incisions and their closure. This subject has been studied by many surgeons and in a general way has been fairly well standardized. There are certain anatomical and surgical principles which govern the character of abdominal incisions.

First.—The incision should give adequate exposure of the field of operation.

Second.—It should injure as little as possible the nerve and blood supply and the function of the muscles of the abdominal wall.

Third.—It should be so planned that primary firm union can be secured which will prevent the opening up of the wound or the later development of a post-operative hernia.

There are certain abdominal incisions which quite fully live up to these requirements and which are generally adopted. These incisions answer well in the great majority of abdominal operations.

In Fig. 1 three incisions are shown in the median line: One between the ensiform and the umbilicus; one between the umbilicus and the symphysis; and a third which has its centre at the umbilicus and a little to the left so as to avoid the round ligament. These incisions are so planned that they are in an avascular territory. They do no injury to the nerve supply and they in no way impair the function of the abdominal muscles. In this same figure you will notice the oblique muscle-splitting incision of McBurney and McArthur used for operations on the appendix and colon and somewhat modified for stone in the central portion of the ureter. I shall later call your attention to an extension and enlargement of this incision which answers well in resection of the right colon and some operations involving the retroperitoneal space. On the left side this same oblique muscle-splitting incision can be used for operations on the lower end of the descending colon, the sigmoid and the left ureter and the retroperitoneal space.

In Fig. 2 I have presented a view of the oblique kidney incision which is so planned that it runs parallel with the nerve supply and which can easily be extended forward so as to expose widely the retroperitoneal space where it is necessary to remove huge kidney tumors or to remove a stone from the lower end of the ureter. This incision can be greatly enlarged by forcibly stretching it apart with the two hands; in doing this the twelfth rib can be fractured at its neck or the ligaments binding the rib to the transverse process ruptured, giving much more room. I shall come back to this incision again in the discussion of the surgery of the retroperitoneal space.

In order to refresh your mind for the moment in regard to the anatomy of

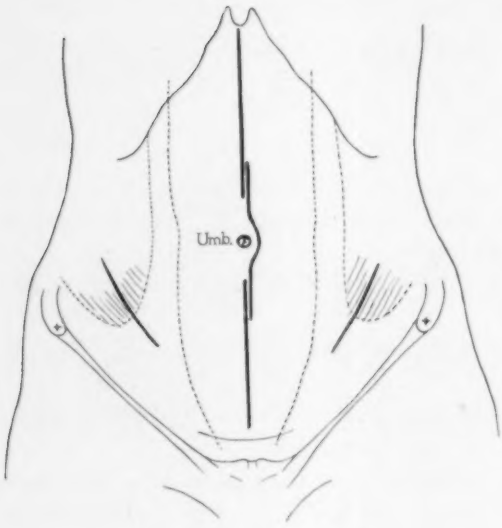


FIG. 1.

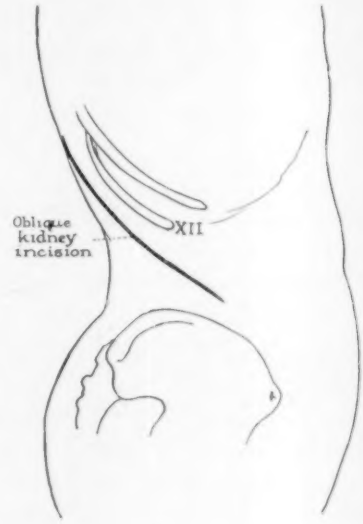


FIG. 2.

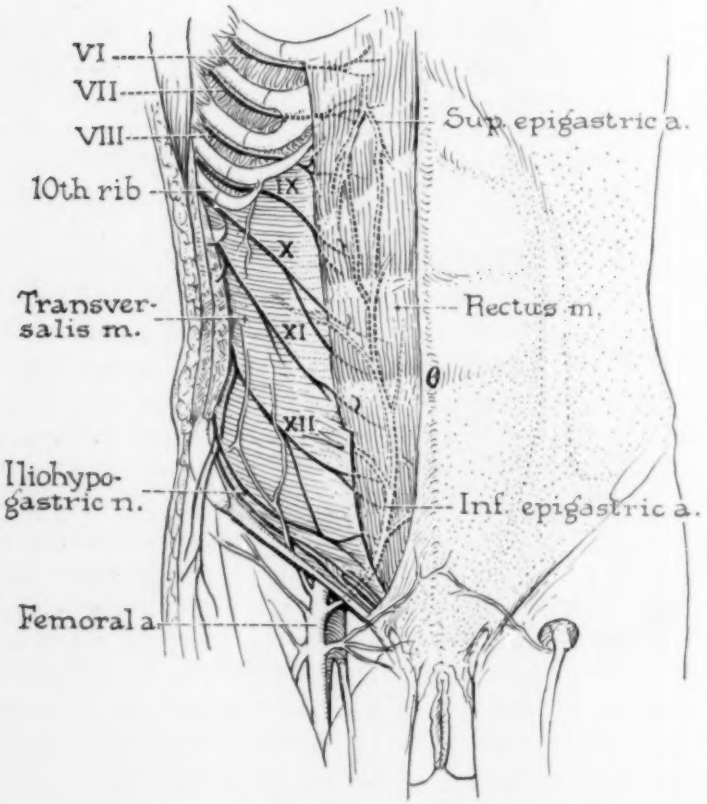


FIG. 3.

the abdominal wall, I show you in Fig. 3 the blood supply and the nerve supply of the abdomen, and in Fig. 4 the muscles of the abdominal wall, and in Fig. 5 the rectus muscle and the arrangement of its anterior and posterior sheaths above and below the linea semicircularis, the semicircular fold of

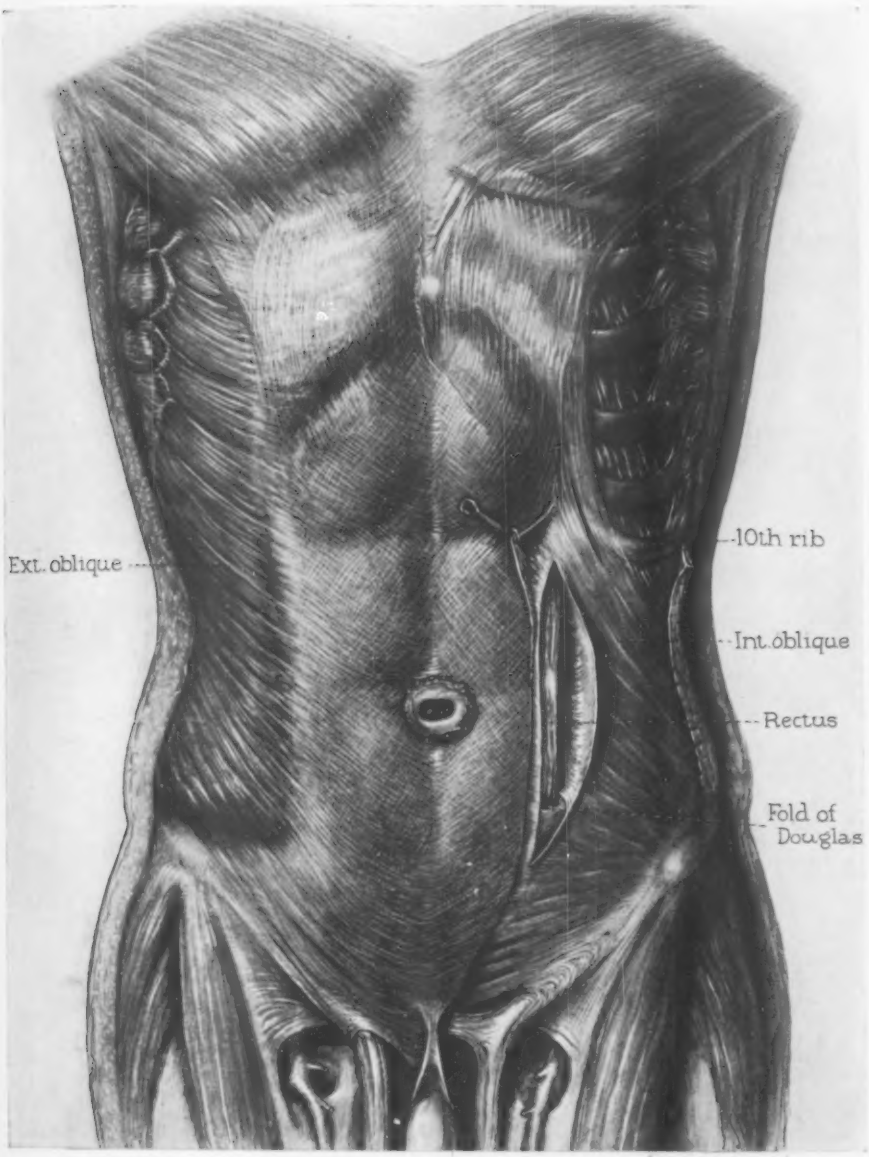


FIG. 4.

Douglas. With these charts of the abdominal wall in mind let us now consider some of the muscle-splitting incisions which have great value in special fields.

First, let me again refer to the McBurney and McArthur muscle-splitting incision for the surgery of the appendix. This was first published by

McBurney. L. L. McArthur, however, had independently developed the same incision and had employed it in a large number of cases and had found that

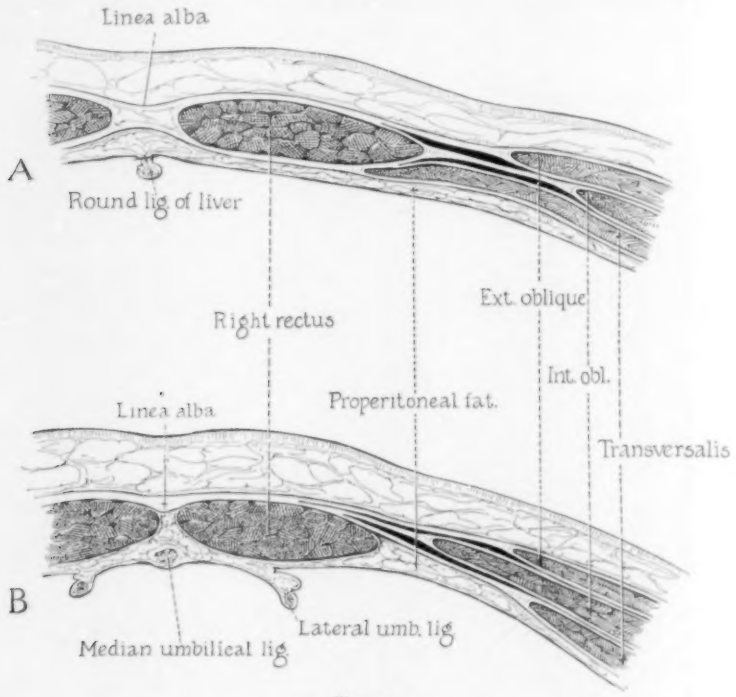


FIG. 5.

it was of special value in the suppurating cases. McBurney at first recommended it in non-suppurating cases. This is so well known that it is not necessary for me to describe it in detail. I have used the incision since 1895

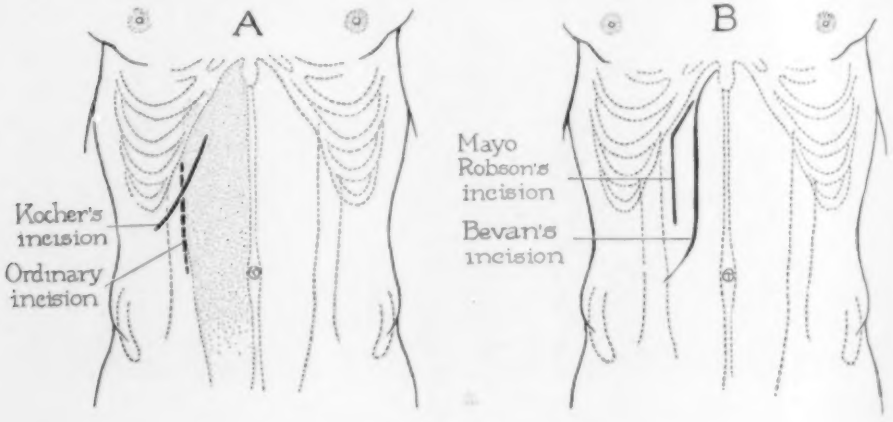


FIG. 6.

and believe that it is planned on sound anatomical and surgical lines and is of great value.

While I was professor of anatomy at Rush in 1897 and attending surgeon

to the Presbyterian Hospital, and much interested in the surgery of the bile tracts, I made a number of dissections to determine the best surgical approach to the gall-bladder and bile ducts, and developed an S-shaped incision at the outer border of the rectus which gave admirable exposure and injured the nerve supply much less than did the Kocher incision or the long vertical incisions at the outer border of the rectus which were then employed. (See

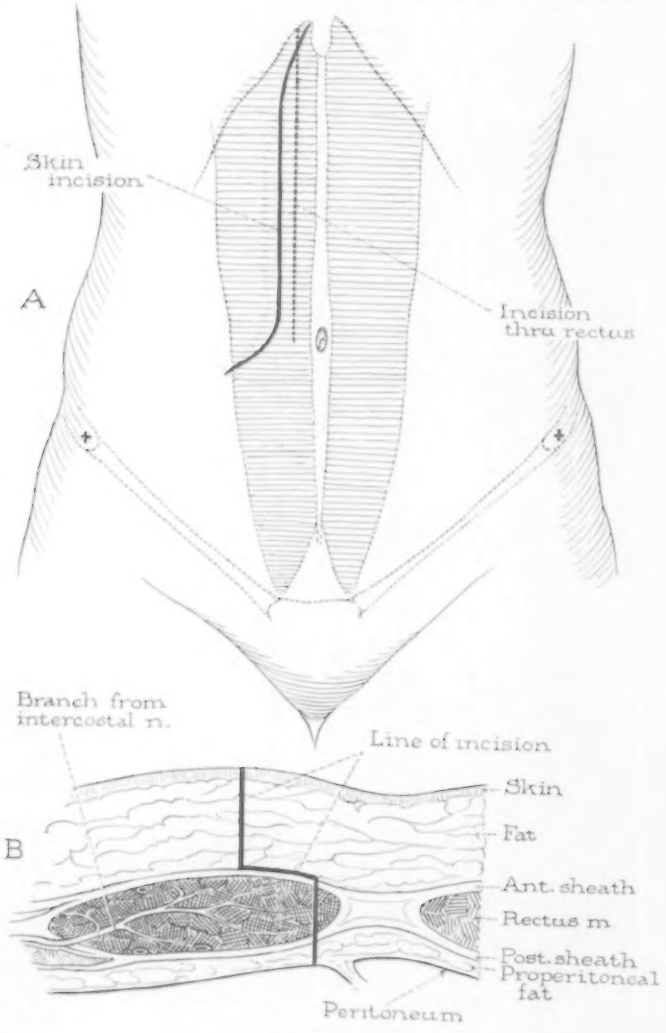


FIG. 7.

Fig. 6A.) I have reproduced the two incisions which were most frequently used up to 1900 for operations on the gall-bladder and bile tracts, namely: the ordinary incision at the outer border of the rectus or in the outer part of the rectus which was most frequently employed at that time, and the Kocher incision which was parallel to the costal arch. I used my incision as originally planned only for a very short time and then modified it at the suggestion of

Robert Weir, by moving the vertical part of the incision inward for two inches so that it was over the middle of the rectus. This incision, which we have used for about thirty years, is shown in Fig. 6B. This plate also shows the Mayo-Robson incision.

In making this incision, at first we split the rectus about the centre; very shortly, however, we split it so as to leave two-thirds of the muscle to the

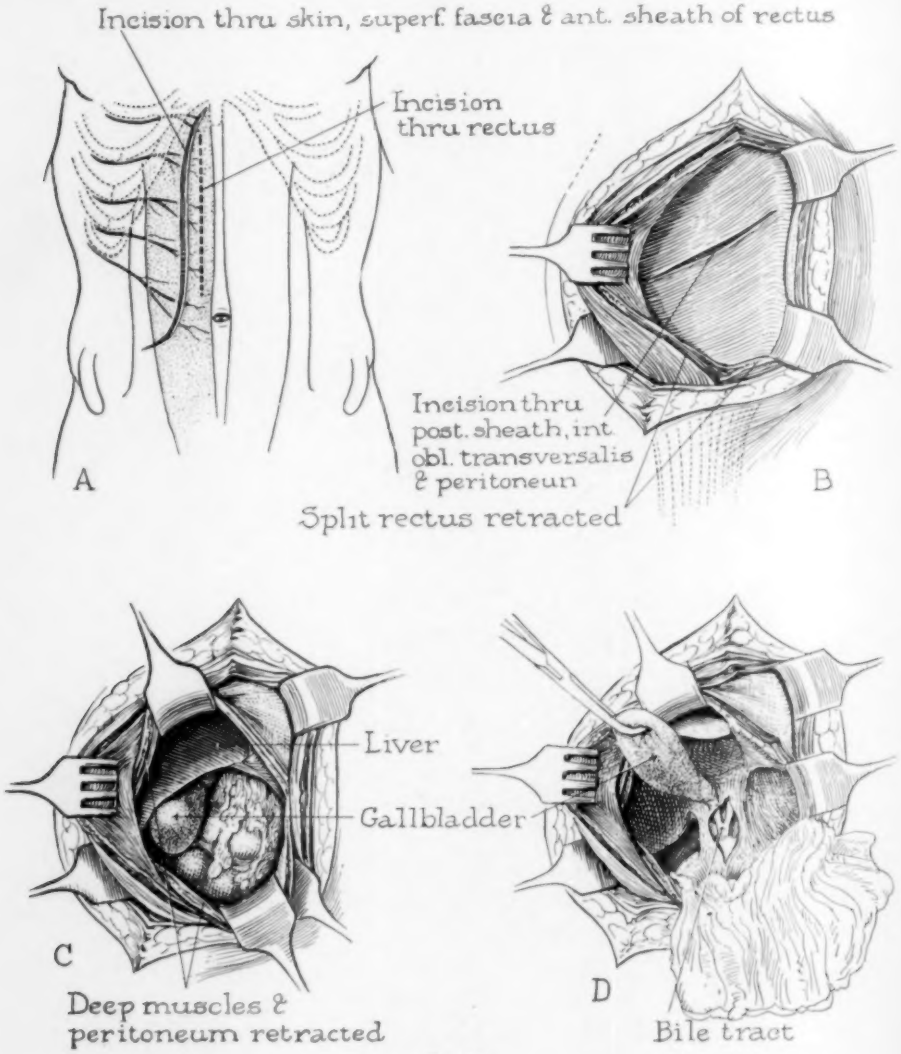


FIG. 8.

outer side and then later so as to leave three-fourths to the outer side, and, finally, a mere ribbon of the rectus one-third of an inch wide was left internal to the incision and for the special purpose of making easier the repair and suture of the posterior sheath. (See Fig. 7.) We have since then experimented with this bile-tract incision in a number of ways. We sometimes

turn the entire rectus to the outer side, making a paramedian incision of it, such as Moynihan uses. We have in a number of cases using the same skin incision adopted a suggestion made by McArthur of splitting the internal oblique and the transversalis parallel with their fibres and at about right angles to the vertical part of our incision. This makes a muscle-splitting incision which gives very good exposure and gives wonderful insurance

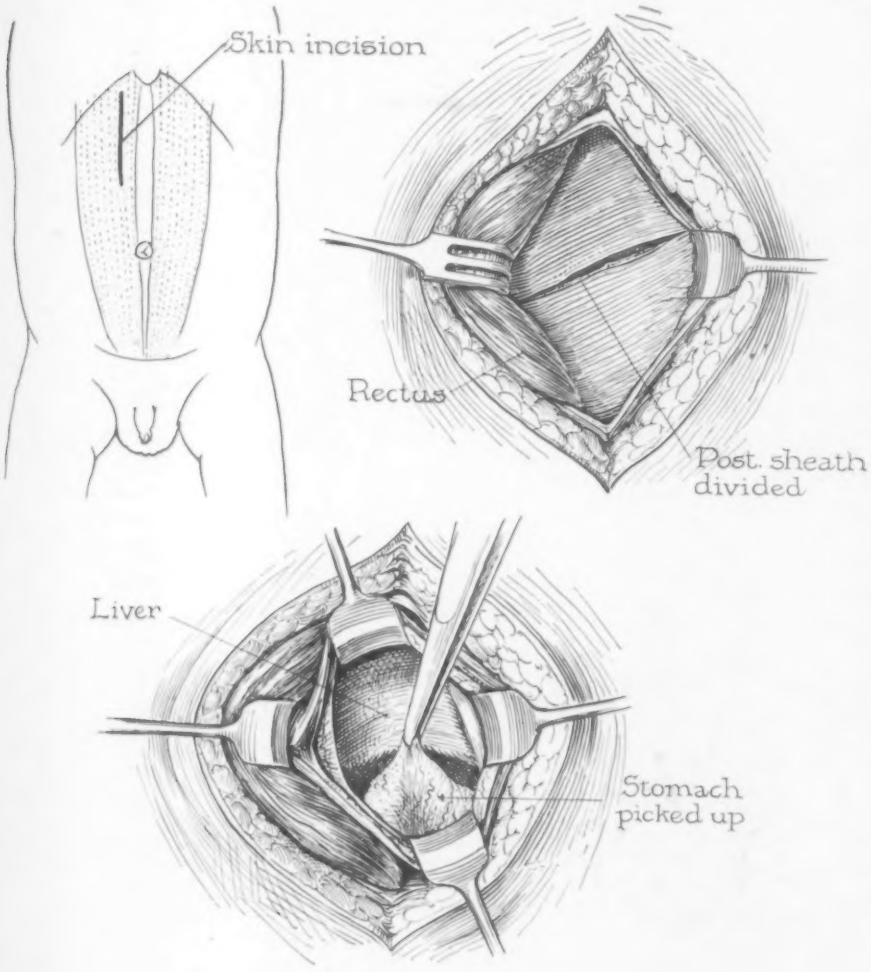


FIG. 9.

against post-operative hernia. This muscle-splitting incision answers very well in cholecystostomies and uncomplicated cholecystectomies and it makes the best possible incision for congenital pyloric stenosis in infants, especially where local anæsthesia is used. Fig. 8 shows the muscle-splitting incision for gall-bladder and bile-tract operations, and Fig. 9 for congenital pyloric stenosis.

Recently, we have been trying out another form of incision for the surgery of the bile tracts which in many ways is anatomically and physi-

ologically, from the standpoint of producing no injury to the blood supply and nerve supply and muscle tissue, and from the surgical standpoint of good exposure of the operative field and of closure, probably the best incision we

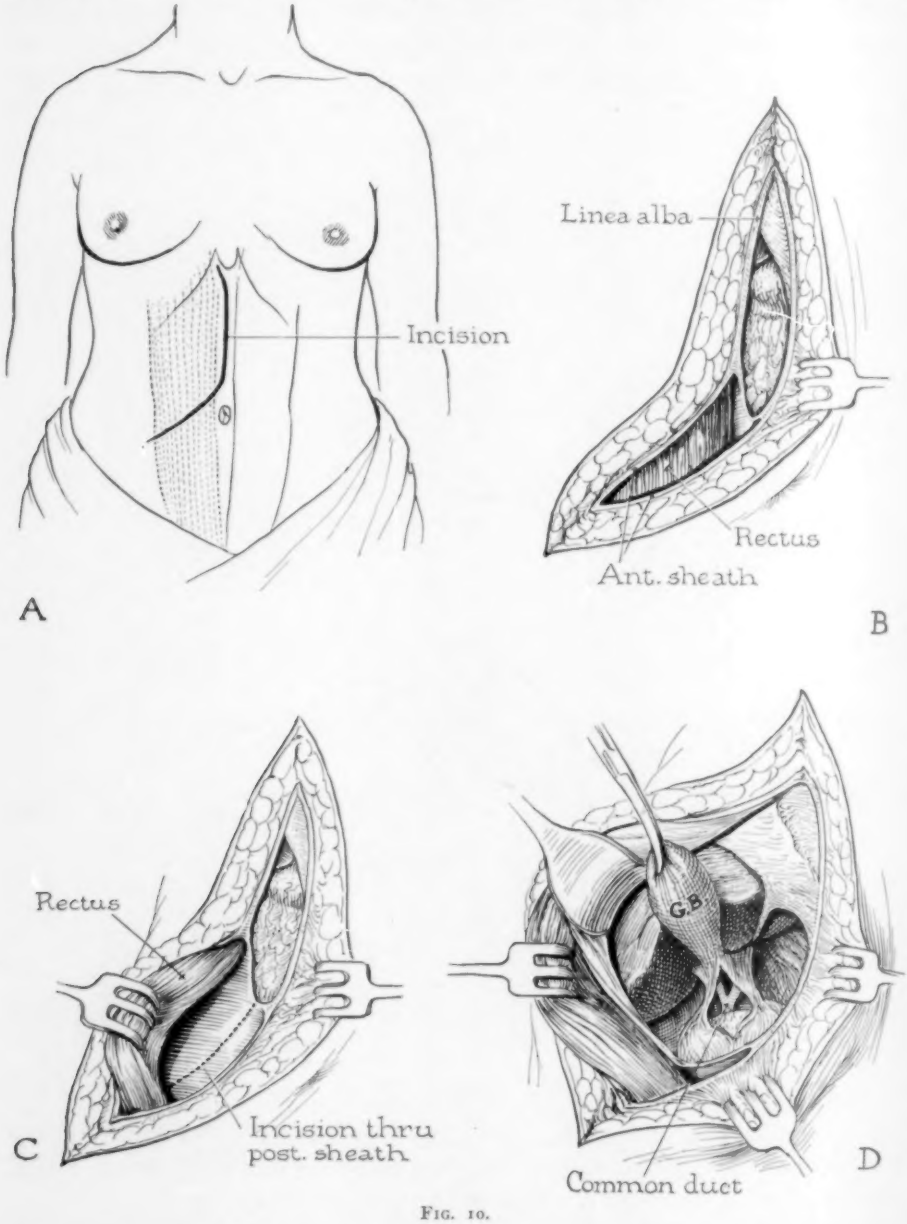


FIG. 10.

have experimented with. We have used it in but a limited number of cases. So far the results are most satisfactory. The incision is shown in Fig. 10. It begins in the angle between the ensiform and the costal arch a little to the right of the median line, passes downward in the linea alba to about an inch

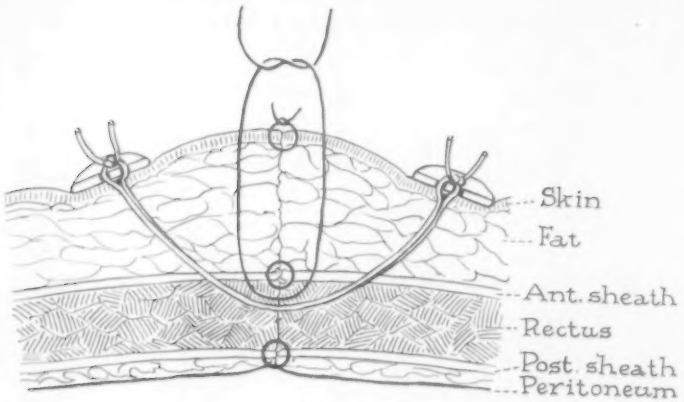
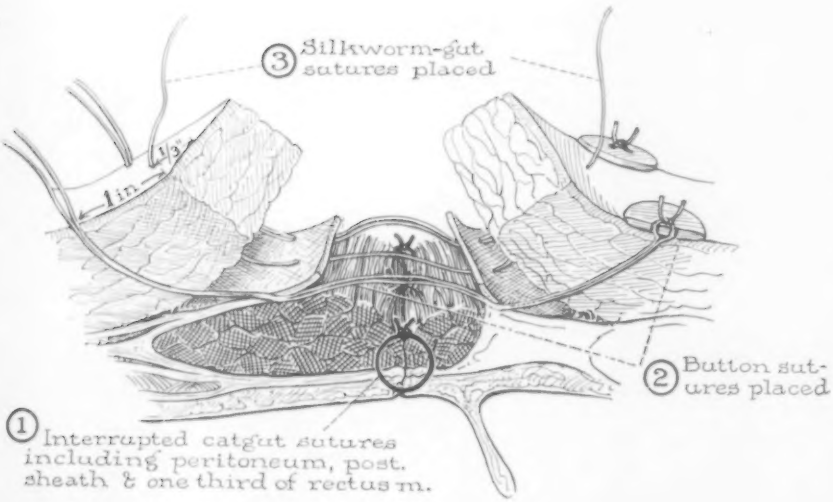

Skin
Fat
Ant. sheath
Rectus
Post. sheath
Peritoneum

FIG. 11.


3 Silkworm-gut sutures placed
1 in.
1/3
2 Button sutures placed
1 Interrupted catgut sutures including peritoneum, post. sheath & one third of rectus m.

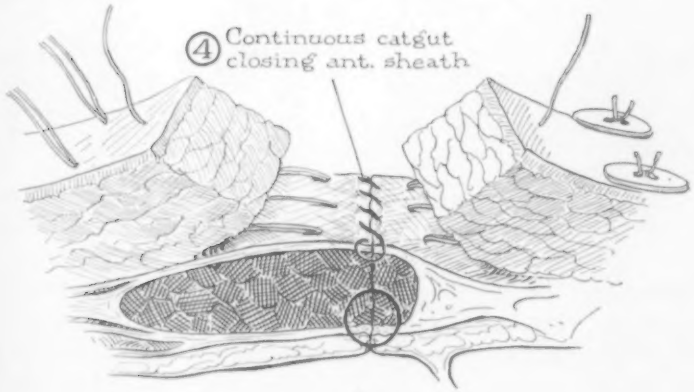

4 Continuous catgut closing ant. sheath

FIG. 12.

above the umbilicus; here it turns outward sharply three or four inches; we divide skin, superficial fascia, the linea alba and the outer sheath of the rectus in the lower curved portion of the incision. This exposes the rectus muscle which is pulled outward with a blunt hook retractor so as to expose the

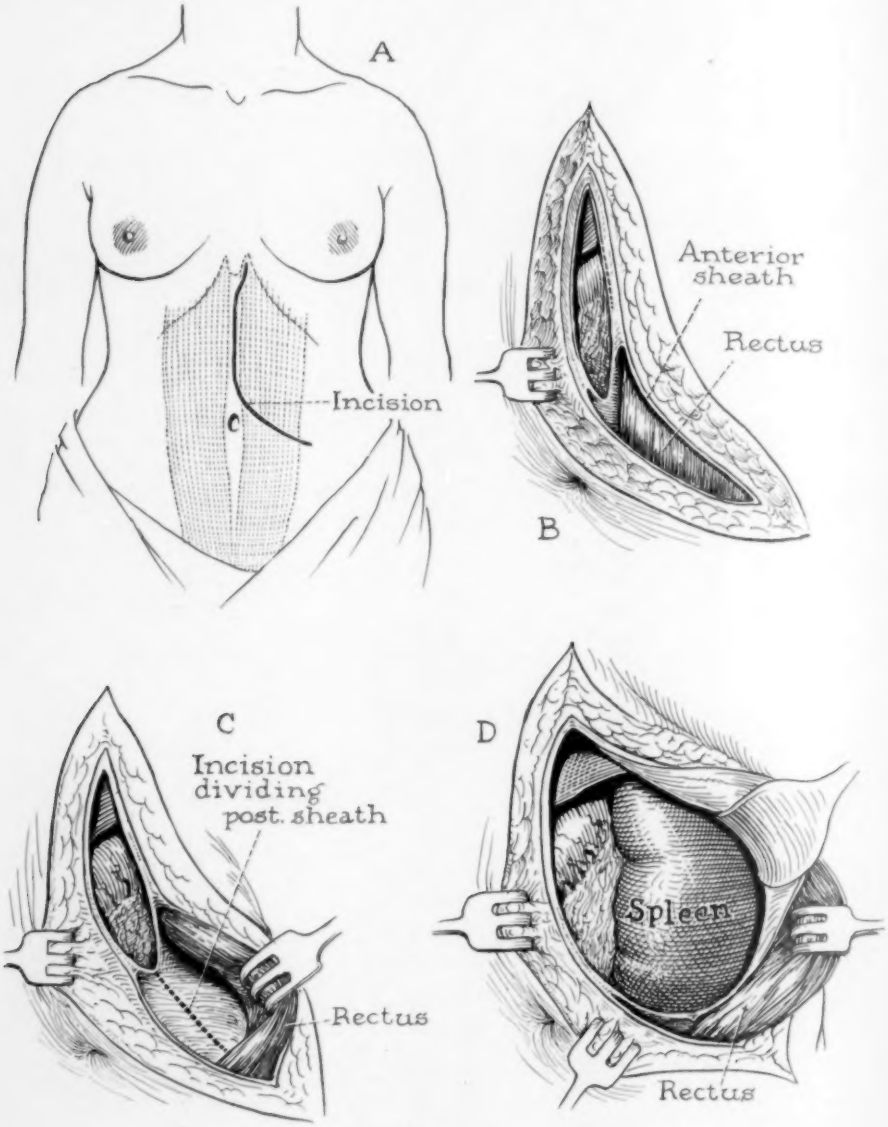


FIG. 13.

posterior sheath of the rectus. This is divided transversely to the extent of three or four inches; this enables us to turn out a huge trap door of the abdominal wall forming the right upper quadrant of the abdomen. In closing, the peritoneum, linea alba and posterior sheath of the rectus in the curved part of the incision are first closed with catgut, the rectus is allowed

to return to its normal position and then the anterior sheath of the rectus is closed with catgut and the incision in the linea alba closed in the usual way.

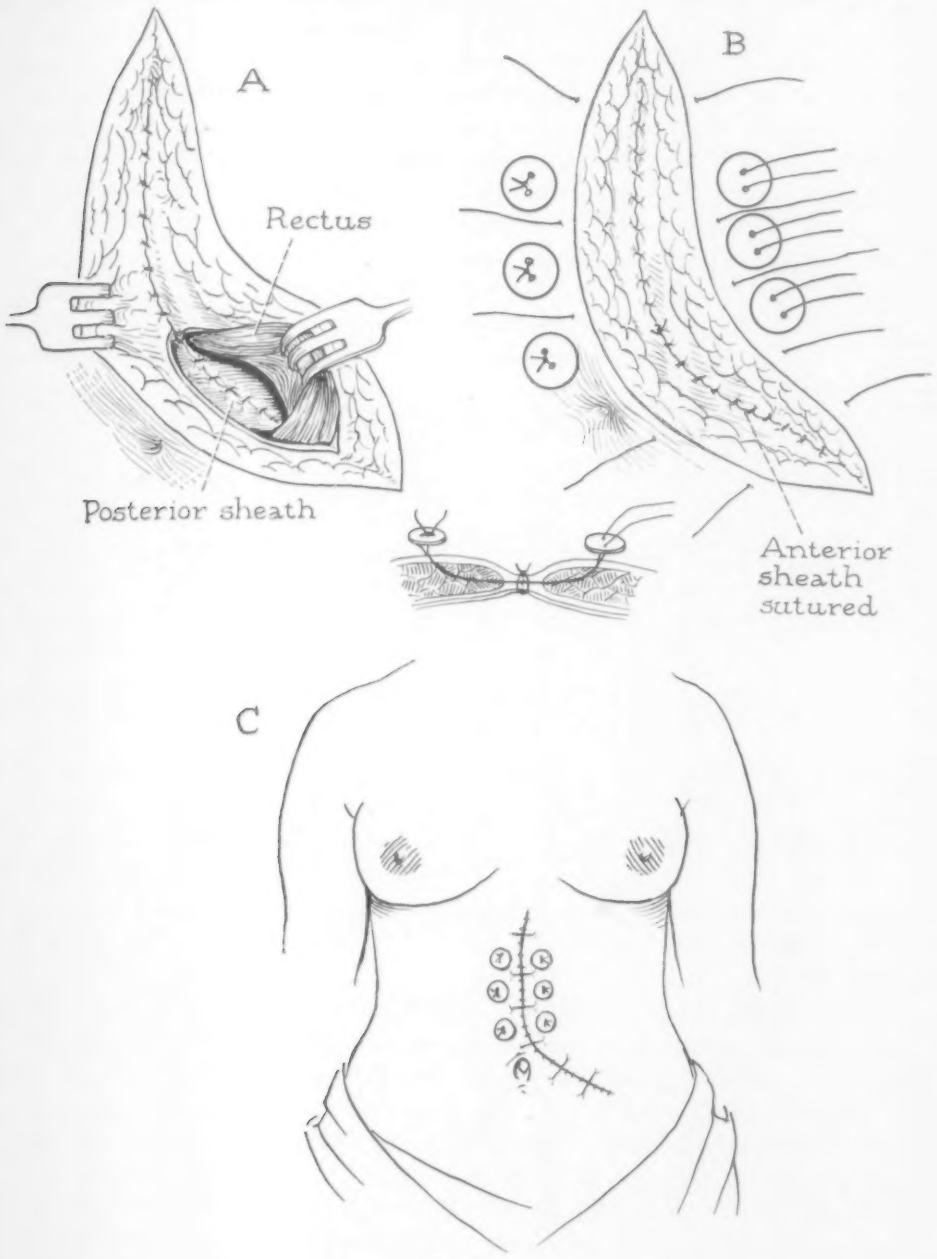


FIG. 14.

I show this closure in the spleen incision. Before closing the incision, a good-sized sharp trocar and cannula are passed from within outward through the outer part of the rectus on a level with the cystic duct and a

moderate-sized French catheter is drawn through the cannula and left in the abdominal cavity for drainage.

I might here describe the plan of closure of these abdominal incisions. (See Figs. 11 and 12.) This is more or less diagrammatic. These plates show, however, very well, the suture method which we employ. First, the peritoneum and posterior sheath of the rectus are closed with rather fine catgut. Then about every two inches a tension-button suture is passed through the skin, superficial fascia and anterior sheath of the rectus. These buttons are about seven-eighths of an inch in diameter and are the pearl buttons of commerce made from mussel shells. They are easily sterilized and kept in alcohol. A large curved needle is threaded with two pieces of silkworm gut; these are passed through two eyes of the button and tied. These sutures are passed about one and one-half inches from the line of the incision. We usually use from three to four of these tension-button sutures; between the tension-button sutures and above and below these we use a single strand of silkworm gut which is introduced one-fourth of an inch from the line of the incision and this passes, as shown in the plates, through the skin, superficial fascia and the anterior sheath of the rectus. The anterior sheath of the rectus is now closed with catgut and the skin with black silk. Metal clamps should not be used to close the skin in abdominal incisions because in some cases where the wound has opened up some of the clamps have been lost in the eviscerated intestines and omentum and have even produced intestinal perforation and death. We have used these tension-button sutures for many years. Their use has practically eliminated the opening up and evisceration in our abdominal wounds.

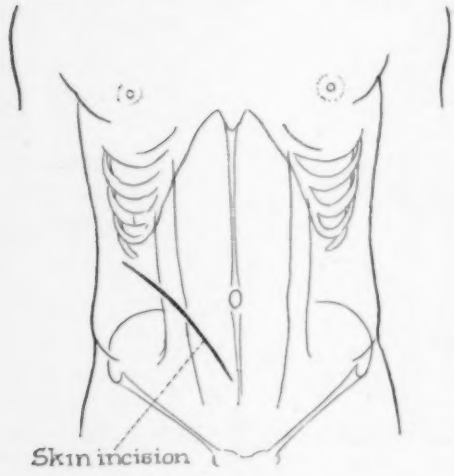


FIG. 15.

The last incision which I have just described for exposure of the bile tracts was first worked out on the left side for exposure of the spleen, for abdominal approach to diaphragmatic hernia and resection of the splenic flexure of the colon. This spleen incision which we are now advocating has been a matter of evolution covering a number of years. We first used the S-shaped incision on the left side which we had developed for the exposure of the bile tracts. Then later we experimented with an incision beginning in the median line and curving outward above or below the umbilicus, depending on the size of the splenic mass, divided the rectus and its anterior and posterior sheath; this gave us wide exposure. Later we found that the division of the rectus muscle was seldom necessary so we now simply divide both the anterior and the posterior sheaths, retract the rectus and obtain in

this way very excellent exposure. (See Fig. 13.) It is true that in many cases splenectomy can be well done with a mid-line incision, if necessary, extending well below the umbilicus. The division of the anterior and posterior sheaths of the rectus in difficult cases, however, is of great help. This incision answers admirably for operations on diaphragmatic hernia at the œsophageal opening and also for operations on the splenic flexure. Fig. 14 shows the method of closure.

I now desire to describe somewhat in detail the large extended muscle-splitting incisions which we are employing on both the right and left sides; on the right side especially for resecting the right colon and on the left side

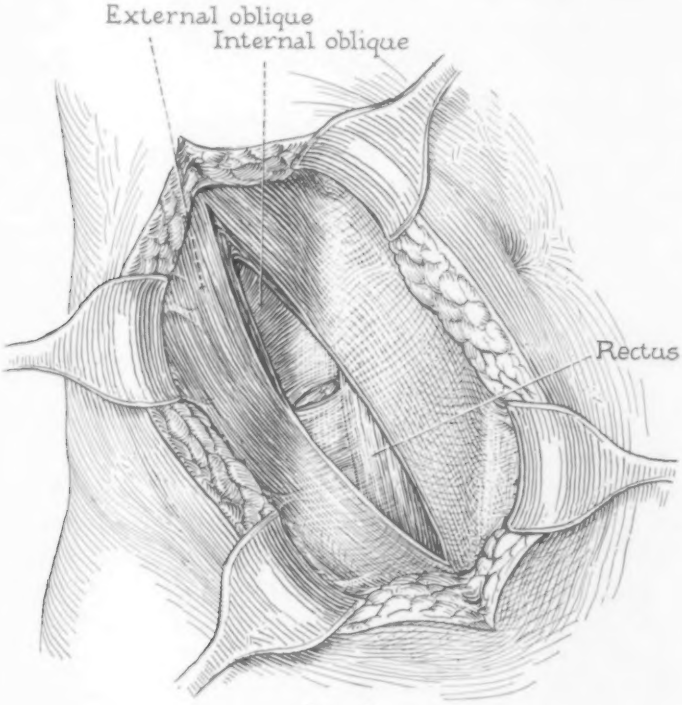


Fig. 16.

for resecting the sigmoid. I shall now describe this large extended incision on the right side. (See Fig. 15.) The incision begins at a point below the tenth rib and runs parallel with the fibres of the external oblique muscle downward and inward, almost to the mid-line. This incision divides the skin, superficial fascia and the external oblique parallel with its fibres. The external oblique is now reflexed, exposing the internal oblique widely; the internal oblique and the transversalis are now divided parallel to their fibres as in the usual McBurney and McArthur incision, and the subperitoneal fat and peritoneum exposed. (Fig. 16.) We now with our two hands, as shown in Fig. 17A, stretch the opening in the internal oblique and transversalis widely and if necessary tear these fibres which enter into the formation of the anterior sheath of the rectus almost to the mid-line. In this

way a very large opening is obtained without any injury to the nerves or blood supply or the muscles of the abdominal wall. Fig. 17B is sketched from one of our cases of resection of the cæcum and ascending colon and hepatic flexure for carcinoma where this incision gave excellent exposure. On the left side this enlarged and extended muscle-splitting incision gives adequate exposure for operations on the lower half of the descending colon and the sigmoid flexure. It does not answer well for the exposure of the splenic flexure. In describing these enlarged and extended muscle-splitting incisions I desire to call attention to the fact that in difficult and complicated operations for appendicitis the usual McBurney incision can be enlarged and stretched in the same way to give very wide exposure. Both Robert Weir and Harrington suggested this years ago.

I desire to describe the method that has been developed in our clinic of handling the cases of opening up of an abdominal incision with evisceration. It was in these difficult cases that we began some years ago to use the large tension-button sutures. In the Ergebnisse der Chirurgie und Orthopädie, vol. xxv, Sokolov of Leningrad presents this subject very fully. He has collected 723 cases from the literature with a mortality of about 33 per cent.

In Fig. 18A we have sketched one of these cases of the opening up of the abdominal wound at the end of twelve days with some omentum and coils of small intestines exposed. An immediate resuture of the wound should be made in the following way: The patient is sent to the operating room; the omentum and coils of intestines covered with a moist abdominal pad. The field of operation is sterilized with iodine. The edges of the incision are infiltrated with ½ per cent. of novocaine solution with 1–200,000 adrenalin; large tension-button sutures are now placed about one and one-half inches from the line of the incision and one and one-half inches apart. The moist abdominal pad is now removed and the eviscerated omentum and intestines held down by a flat metal retractor. (See Fig. 18B.) Beginning at one end of the incision the button-tension sutures are first drawn tightly together and tied. As the sutures are tied the flat metal is gradually withdrawn. The wound is now dressed with moist boric gauze and held firmly in place by a scultetus bandage. This dressing should be changed each twenty-four hours; no attempt should be made to close the skin tightly with skin sutures as it is desirable to obtain a certain amount of drainage between the tension-button sutures. It is as a rule not wise to use any gauze tampon or rubber drainage in these cases and it is not wise to attempt to sterilize the eviscerated abdominal contents, and it is as a rule a mistake to use a general anæsthetic. Following this simple method most of our cases have gone on to a recovery.

I desire finally to discuss the oblique incision for the exposure of the kidney and ureter and the structures in the retroperitoneal space. This field has recently been very fully covered in an article by Fritz Härtel, of Berlin, in the Ergebnisse der Chirurgie und Orthopädie, entitled: On the Surgery of the Retroperitoneal Space and the Dorsal Peritoneum. I have, myself, been for some years interested in this field. Küttner, of Breslau, in the Trans-

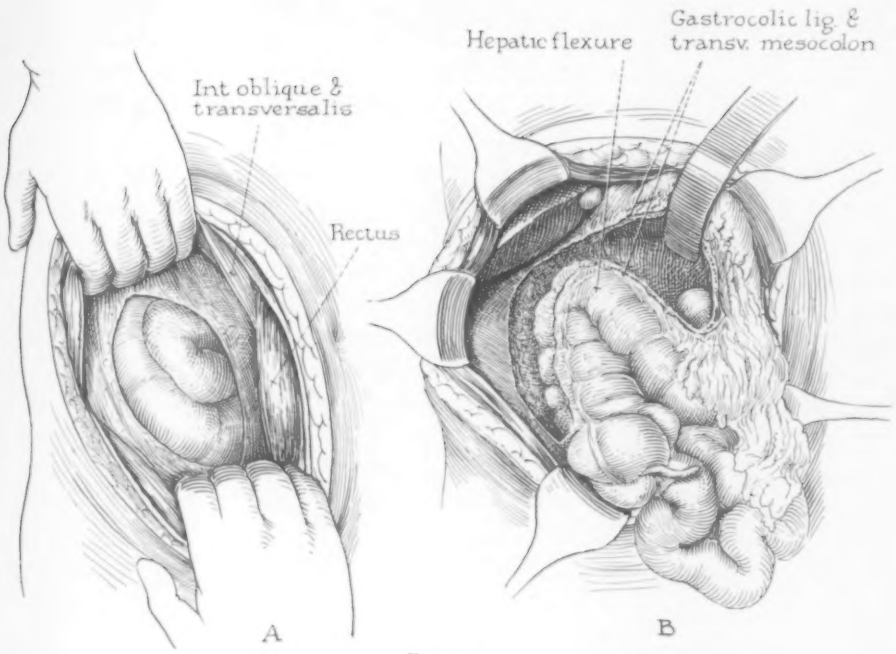

Int oblique &
transversalis
Rectus
A
Hepatic flexure
Gastrocolic lig. &
transv. mesocolon
B

FIG. 17.

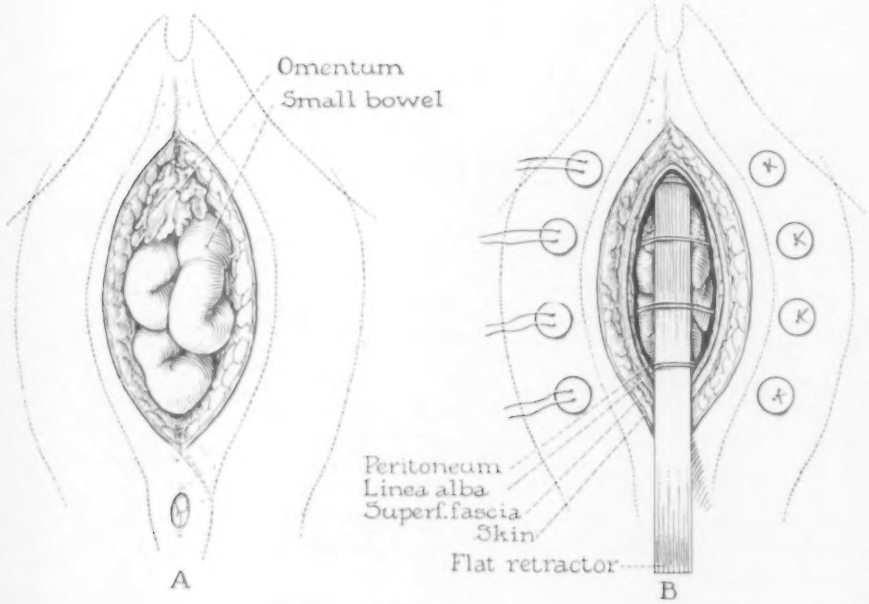

Omentum
Small bowel
A
Peritoneum
Linea alba
Superf. fascia
Skin
Flat retractor
B

FIG. 18.

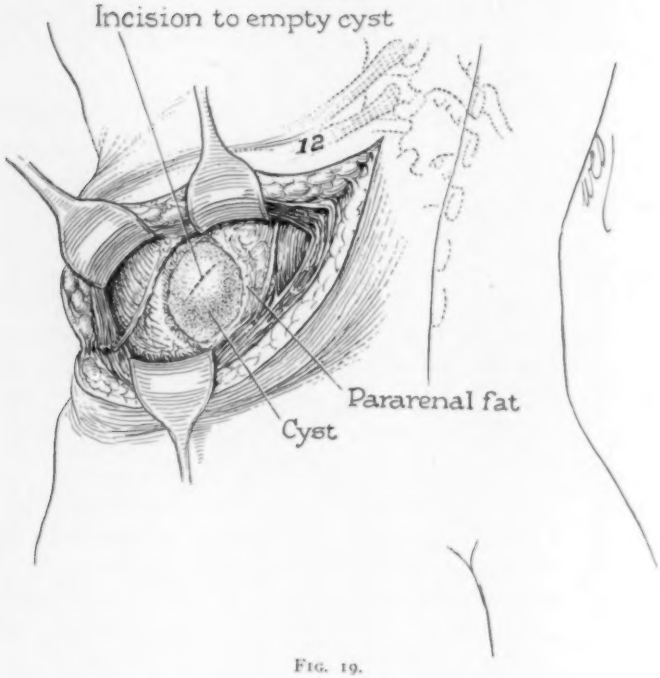

Incision to empty cyst
12
Pararenal fat
Cyst

FIG. 19.

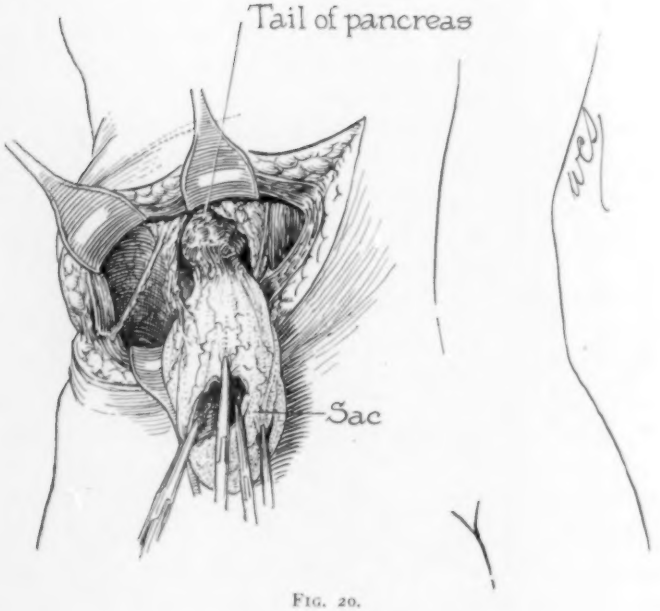

Tail of pancreas
Sac

FIG. 20.

actions of the German Congress for Surgery last year, in discussing Härtel's paper, states that for years he has employed the retroperitoneal approach in many operations. He advocates it in some resections of the ascending and descending colon, in some splenectomies, in some pancreatic cysts, and in draining of certain pancreatic infections. I believe that the retroperitoneal approach has a wider field of usefulness than we have up to the present time realized. I have employed it in various types of retroperitoneal and subphrenic abscess, in resection of the ascending and descending colon, in lesions of the kidney and ureter, in various types of retroperitoneal tumors and in injuries of the duodenum. Härtel regards it as the best approach in splenectomy. I have recently employed it in removing a large cyst of the pancreas where I was surprised and delighted to find that it gave very satisfactory exposure and where the operation was completed without opening the general peritoneal cavity. (See Figs. 19 and 20.) I believe that we should cultivate more thoroughly the great possibilities of this retroperitoneal approach.

The making of abdominal incisions and their closure is a very fascinating study. It is by no means a closed chapter. I have in this brief paper attempted to present the results of the research in this field which we have carried on in our own clinic.

Discussion.—Dr. Chas. Gibson (New York City) said that failures in procedures are not necessary in any case of large ventral incisional hernia. He said that with confidence from a very considerable experience in which he had never had anything approaching failure.

The procedure is described by him in a paper read before this Association at St. Louis in 1920, called, The Fascia Flap Operation for the Cure of Large Ventral Hernias. At that time he reported his only failure, in a man who had been operated on six times before unsuccessfully and who had a hernia running from the ischium to the pubis. His failure was in a small gap which the man tolerated well. That was his last failure.

The great bulk of these cases have been operated on, by all kinds of procedures, by surgeons, some of them of great skill. Many of these patients have been very large and obese. One man he presented at various times before the New York Surgical Society, and others also have very typical cases; no patient died. He had never refused a single patient. He believed from his personal experience that there is not a single case of ventral hernia that cannot be cured by careful, sometimes very laborious reconstruction of the abdominal wall and the so-called fascial flap.

Of course, the fascial flap is only a step in the whole thing. One must unsnarl the whole mess and be able to release such muscles as remain. A good many are destroyed in straightening them out, but that can be done very well, but still there remains the fascia, and he had made an incision on either side for a suitable size and suitable length. In the average cases the releasing incision would be three or four inches, and situated an inch and a half to two inches from the mesial line.

Almost always when he had spoken on this subject somebody had felt very anxious and very worried lest at the site where the releasing incision was made there should be a weakness. None of these cases has developed this horrible, theoretical weakness. Careful work in any of these hernias can be absolutely assured in something approaching 100 per cent. of the cases.

Dr. Ellsworth Eliot, Jr. (New York City) emphasized the advantages of closing hernial orifices, the edges of which cannot be approximated and overlapped without

undue tension, with completely detached segments of fascia lata. One of the largest orifices of this kind followed the sloughing of the entire anterior abdominal wall, both above and below the umbilicus, the result of a wide infection following a pan-hysterectomy at the hands of another surgeon. In this instance a large segment of fascia lata, superimposed upon the properitoneal tissues, was placed in the defect, the border of the segment being sutured to the deep surface of the freshened lateral aponeurosis an eighth of an inch from its edge, which in turn was sutured a corresponding distance to the anterior surface of the transplant, giving the appearance of a "double-breasted coat." The suture material was chromic gut. The skin and subcutaneous tissue were then brought together over the fascial flap.

Prompt union followed and for three years following, at the end of which time the patient succumbed to a pneumonia, there was no indication of a recurrence or of any tendency to an enteroptosis.

Dr. Howard Lilienthal (New York City), in the operation of splenectomy, especially when the organ is large, preferred an incision beginning beside the xyphoid running downward paramedially as far as seems necessary, then making an incision to connect with the upper end of the first one and passing close to the costal arch as far as the seventh or eighth rib-cartilage. The flap thus formed can be turned downward and the entire region can be beautifully exposed by retraction of the costal arch upward and outward. If necessary one or two ribs may be divided for simplicity in exposure. None of the lower intercostal nerves is interfered with, nor is there any paralysis of the recti muscles; the nerves which are cut unite nicely. He had had one patient who went through a pregnancy and confinement without undue stretching of her abdominal wall and with perfect recovery of abdominal function afterward.

Hernia is likely to occur in inverse proportion to the distance of the wound from the lowest part of the abdomen.

The incision described by him is through the fascial tissue parallel with the costal arch and permits excellent repair by suture.

When he first did this operation it was original with him but he had since found that others have used it.

Dr. William B. Coley (New York City) felt very much as Doctor Gibson does about there being a small number of cases in which it is necessary to use a method of this sort. He likewise had succeeded in closing very large abdominal openings by overlapping the fascia and using kangaroo tendon which is really a heterogeneous fascial suture.

He had been very greatly interested in the operation which Doctor Gallie brought out over ten years ago for treatment of large recurrent and direct hernias by means of living fascial sutures.

The first Gallie operation at the Hospital for the Ruptured and Crippled was performed by Dr. Bradley L. Coley. The method was quickly adopted by the other members of the Hernia Division, and up to the present time 1,060 Gallie operations have been performed at this hospital, as follows: *First series.*—Autogenous (human fascia), 798, with sixteen (2 per cent.) deaths; sixty-six (8 per cent.) infections; forty-three (5 per cent.) recurrences during first year; and forty-four (15 per cent.) recurrences after the first year. *Second series.*—Homologous (human fascia), seventy-five, with five (7 per cent.) deaths; nine (12 per cent.) infections; five (7 per cent.) recurrences during the first year; and six (30 per cent.) recurrences after the first year. *Third series.*—Heterologous (ox fascia), 195, with one (.5 per cent.) deaths; eighteen (9 per cent.) infections; sixteen (8 per cent.) recurrences during the first year; and fifteen (18 per cent.) recurrences after the first year. The total recurrences were 129 (29 per cent); and the total deaths twenty-two (2 per cent.)

These figures show that the fascial-suture operations have had a mortality about

six times as great as that found in a series of 3,000 consecutive herniotomies at the Hospital for Ruptured and Crippled during a period of three years and nine months prior to our first use of fascia, the mortality being 1 in 300 cases in the earlier series as opposed to 2 in 100 cases in this series of fascial suture cases.

The percentage of infections in the fascial-suture cases is not appreciably higher.

The recurrence rate seems surprisingly high (29 per cent. of all cases of all types). However, these figures are based on a careful follow-up examination by various members of the visiting staff of the two hernia divisions of the hospital, and they are obtained by taking the number of known recurrences and figuring the percentage based only on those cases followed more than one year. If the total number of known recurrences were figures on the basis of the total number of operations performed, the percentage of recurrences would fall to nearly one-third of the figures as given.

Percentage recurrence rates should, however, be figured only on the basis of followed cases.

It is regrettable that but 36 per cent. of the total number of cases operated upon could be traced longer than one year. Conditions of life among the clinic class in a large city, ignorance, indifference, and the floating character of our population are obstacles which can be met with only partial success.

Dr. J. Tate Mason (Seattle) called attention to the bayonet type of incision that was suggested some years ago. It is especially useful where one has difficulty in getting adequate exposure in the upper abdomen. There are no muscle fibres cut and very few nerves severed, and it gives the greatest exposure one can obtain in the abdomen because it embodies a longitudinal and a transverse incision in one. The incision is begun high up on the inner third of the left rectus, is carried down to within two and one-half centimetres of the umbilicus, and is then brought transversely over to the right rectus and continued down the inner third of this muscle for three or four centimetres or as far as one needs exposure. The anterior sheaths of the muscles are then opened and the muscle fibres retracted laterally.

The only criticism that might be made would be as to the possibility of a post-operative hernia through the transverse part of the incision. He did not know at this time how many of these incisions they had performed, but in the fifteen years since this type of incision has been used they had had very few hernias. The transverse part of the incision is closed first. This procedure is based upon Dr. W. J. Mayo's operation for umbilical hernia, which he described before the American Medical Association about 1903, in which the transverse incision is imbricated. This is the only part of the operation where one needs to use particular care. He emphasized the importance of closing this part of the incision first.

Dr. W. E. Gallie (Toronto) said that in presenting this method of closing large hernias he should make it clear that it is one that is not often necessary. He had found, however, that his friends had accepted the various papers he had written on hernia as more or less of a challenge and had sent him cases the like of which he had never seen or heard of. As a result he was forced to devise a method which would hold out a reasonable hope of cure.

He had no doubt there are lots of other ways of curing difficult hernias besides the one he had described. He must say, however, that he was not so much interested in them as in his own method.

Dr. Arthur Dean Bevan (Chicago) said that he understood that Doctor Gallie employs his method in very difficult cases. He himself had done, as Gibson has done in the ordinary post-operative hernia, and had used the fascia that was at hand, without transplanting.

He had, however, introduced one important point in connection with the use of that fascia and that is what they call their vertical imbrication. Instead of imbricating

one layer above the other they very often in the difficult post-operative hernias make a vertical imbrication with three rows of stitches, so bringing a broad surface of the fascia in contact and holding it in contact with three rows of sutures. They have really gotten, by such a vertical imbrication, better results than with anything else.

He was sure, however, that with difficult cases, with destruction of the fascia, that the method that is presented by Gallie is very much worth while. I think it really enlarges our ability to handle some of these difficult problems.

In regard to Doctor Lilienthal's modification of the Kocher incision, if he will take an anatomy, he will find that his incision divides most of the nerves of the abdominal wall.

The problem which they had been working on was to attempt to make incisions which would give adequate exposure without any injury to the nerve supply. It is not alone paralysis; it is the trophic changes which occur which favor hernia, and not only the nerve supply but also the blood supply. There is really no reason any longer, and there never has been very much, to make these tremendous incisions which are so destructive of the important structures in the abdominal wall.

HERNIA OF THE URETER

By Alexis V. Moschcowitz, M.D.
of New York, N. Y.

I doubt that it will create much controversy if I assert that the operation for the radical cure of hernia is one of the most frequent, if not actually the most frequent, operation of present-day surgery. So frequent indeed, that the operation has lost caste and has come to be looked upon as a sort of minor procedure and one which in many clinics is often relegated to one of the junior assistants. I have always been averse to this shiftless method of dealing with the hernia problem and on many an occasion have so expressed myself in vigorous and sometimes undiplomatic language. This difference of opinion arose because of the undeniably frequent recurrences even in the hands of expert surgeons. I was therefore rather gratified to find that so eminent a surgeon as Schmieden as recently as 1929 (Archiv für Klinische Chirurgie, vol. clvii, p. 122) at a meeting of the German Surgical Society expressed his views regarding this subject in the following words: "The operation for inguinal hernia is looked upon as simple and easy; it is often treated with little respect and is left to the beginner, a frequent cause of the bad result. The surgeon who desires good results must look upon the operation as one of importance. I do not consider the operation easy. . . . Let us all again look upon the (well-executed) operation as a (surgical) masterpiece." If this is true, and, as far as I am concerned, I agree with Schmieden unequivocably, of the simple and uncomplicated herniæ in which only the question of recurrence arises, how much more true is it for herniæ with complications of one or another nature! I have personally called attention to some of these. Thus for instance, in describing the pathogenesis of herniæ of the large intestine in general and of sliding hernia in particular (Annals of Surgery, vol. lix, p. 610), I made the statement that there is hardly any operation that may tax the patience and technic of the best-equipped surgeon more. In another part of the same article, when discussing the frequency of sliding hernia, I ventured the opinion that the paucity of case reports is very probably due to the fact that "the operator did not wish to be reminded of a rather unpleasant experience."

When I operated upon Case III of this series of hernia of the ureter, I was so impressed with the difficulty of the operation and with the possibility of injuries of the ureter, that I then and there determined to review both my own and the published cases in order to again call attention to same. The real motive, however, was furnished me when I found, upon mentioning my latest case of hernia of the ureter to some colleagues, that they chided me and denied not only the occurrence but even the possibility of this variety of hernia. No one can deny the rarity of this form of hernia, the possibility is

proven, however, by my own cases and by several well-authenticated case reports in the literature both here and abroad.

The pathogenesis of ureteral hernia is that of sliding hernia in general, which I have fully described in the article previously referred to. In other words, we find among ureteral herniæ, just as among all sliding herniæ, two varieties, namely, very large herniæ which have been formed by a pulling mechanism and in which a rather large section of the ureter has become herniated, and small herniæ, which are produced by the so-called pushing mechanism and in which the herniated portion of the ureter is correspondingly short. The latter usually occur in combination with hernia of the bladder and only the very lowest portion of the ureter becomes involved in the hernia. Not infrequently, the latter are of the femoral variety. In reality, there exists also a third variety which may be called an intermediate or mixed group, in which it is difficult to determine the exact mechanism of production. I have in mind one such instance in my personal experience, in which the hernial contents were rather manifold, namely, an ovary and tube with a cornu of the uterus, the sac was made up principally of the unfolded broad ligament behind which there was noted a section of the ureter about two inches in length, very probably the juxtavesical portion of same.

The question that interested me much more, however, was just why there exists so much scepticism in the minds of surgeons of repute and experience even as to the possibility of the occurrence of a hernia of the ureter. This interesting phase is very likely due to the generally prevailing impression that the ureter, being located entirely extroperitoneally and therefore not having a true peritoneal coat, has nothing further to do with the mobility or movements of the peritoneum. But this prevailing impression is entirely erroneous as I have been able to prove to myself, not only in operations upon the ureter, but also in the dissecting room. I have found, namely, that the lower abdominal and pelvic portion of the ureter is intimately adherent not, as one might surmise, to the structures of the posterior abdominal and pelvic parietes upon which it lies, but to the peritoneum which covers it in front. If this were not the case, then hernia of the ureter would be an absolute impossibility; but as it is in reality, the position of the ureter is analogous to the position of the ascending or descending colon—the only difference being that the peritoneal covering of these structures is somewhat more closely attached to the underlying muscular coat than it is to the ureter.

If this elementary but nevertheless fundamental point in the surgical anatomy of the ureter and its relationship to the peritoneum is thoroughly appreciated and understood, then the formation of a hernia of the ureter becomes not only plausible and possible, but in combination with certain definite circumstances, even probable. The presence of a sliding hernia of the ascending or descending colon has so often been demonstrated by operative findings that when one considers the close proximity in the retroperitoneal space of these structures to the corresponding ureters, it is only surprising that the ureter is not a more frequent finding in these.

It is but a very short distance from the peritoneal sac of a sliding hernia of the descending or ascending colon to the peritoneal sac of a hernia of the cæcum or sigmoid flexure, necessarily of the non-sliding variety. Let us now assume for the sake of argument that the latter hernia has increased just a trifle more, and let us assume furthermore, as it really is, that the previously described relationship of the ureter to the peritoneum is correct, then it will be readily seen how the ureter will be dragged down with any further increase in the size of the hernia. If that is the case, we may have a non-sliding hernia of the cæcum or lowermost portion of the ileum in combination with a sliding hernia of the ureter. As I have developed the formation of this hernia, it will be readily seen that this particular hernia must be of large size, and, in consequence, must have been formed by the so-called "pulling" mechanism.

For the formation of a hernia of the ureter by the so-called "pushing" mechanism, we must assume favorable relationship and proximity of the bladder and of the adjoining portion of the ureter to a hernial opening. A knowledge of anatomy will at once suggest that this is much more probable in femoral and direct inguinal hernia than in oblique inguinal hernia, though the latter is by no means excluded. It is surprising how frequently the bladder is found in all three of these by the careful dissector; on the contrary, when isolating the sac for a very high ligation, I hardly ever fail to visualize the fatty covering of the bladder. If the postero-lateral part of the bladder is extruded, it cannot be surprising if a small segment of the ureter also becomes extruded. This would therefore be a sliding hernia of the ureter by the "pushing" mechanism.

The treatment of a hernia of the ureter does not differ from that of any other hernia and very little need be said upon the subject. The only important point during the operation is to recognize the ureter when seen and if recognized, not to injure it. No specific directions can be given regarding the recognition, excepting the self-evident one, which is applicable to every hernia operation and for that matter to every operation whatever its nature, namely, not to cut or divide anything unless one knows absolutely what that particular structure is. In operations for hernia of the ureter, in particular, caution must be exercised with any cord-like structure which may be encountered upon the extraperitoneal surface of the sac. In the order of their frequency, these can be only the vas deferens, round ligament, the tube, the obliterated hypogastric artery, the vermiform appendix and the ureter. I believe the differentiation of the first three is so characteristic that it need not detain us further. The physical characteristics of the ureter are not particularly marked. Above all, it lacks the peculiar wiriness of the vas deferens and of the obliterated hypogastric artery, and, odd as it may appear, in the few cases it has been my good fortune to encounter it in a hernia, it appeared to me to be rather more ovoid than circular, but this may have been due to haste in my observation, and no one will blame me for haste in the course of a rather extensive and strenuous operation. The important point to be emphasized is to remember not to injure, or, worse still, divide the odd-looking cord-like

structure on the posterior surface of the hernial sac. It may appear peculiar that I lay so much stress on this point, but I am constrained to do so because it is an accident which has happened in the most expert hands, has cost dearly, even life, and may happen again. The proper way of dealing with the ureter is to dissect it with great care off the external surface of the sac and to replace it as well and as neatly as possible into the retroperitoneal space of the abdomen, a maneuvre much aided by elevating the patient into Trendelenburg's position. In one of my cases (CASE III) so large a section of the ureter was prolapsed that I feared a kinking of it when replaced haphazardly into the retroperitoneal tissues, an accident I obviated by placing the patient after the operation into a rather exaggerated Trendelenburg's position for a few days.

Watson (Hernia, S. V. Mosby Company, St. Louis, 1924) in discussing hernia of the ureter gives a complete bibliography of the subject up to the date of his publication to which those interested are referred. He states that in 1923, he collected from the literature forty-seven cases of ureteral hernia. I have been unable to find any additional cases reported since that time. I have encountered four cases of ureteral hernia which would bring the total up to fifty-one.

My cases are the following:

CASE I.—Deborah L., fifty-five years of age, was admitted to Mt. Sinai Hospital in the service of Dr. Arpad G. Gerster to which I was then attached, September 21, 1913. She gave a history of the existence of a left-sided hernia of several years' duration which had given symptoms of strangulation, namely, generalized abdominal colic, nausea, vomiting and complete obstipation for four days. Physical examination revealed the presence of a strangulated femoral hernia. I operated upon her, as I am accustomed to doing, through an inguinal incision. The operation revealed a strangulated but viable Richter hernia of the small intestine. In clearing the sac, the ureter was discovered skirting along the outer surface of the sac running inward in order to reach the bladder. The ureter was carefully dissected away from the sac, replaced and the radical operation finished in the customary manner. No untoward symptoms arose and patient was discharged well, October 18, 1913.

CASE II.—I greatly regret that after a very strenuous search of the histories of Mt. Sinai Hospital, I failed to find the history of this patient. My only record of it is a short reference in Johnson's Operative Therapeusis, vol. iv, p. 68, where, in the chapter on ureteral hernia, I mention two cases. The first case is Case I just reported and the second case is the present one. Although I do not possess the exact history, the important points are so vividly impressed on my memory that I may be permitted to quote from it. The patient was a young woman afflicted with a hernia on the right side, in which on account of the peculiar sensitiveness, a pre-operative diagnosis of an ovarian hernia was made. I was much gratified when I found that the operation verified my pre-operative diagnosis. The further development of the operation revealed in addition to the ovary the presence of the tube and the right cornu of the uterus. The posterior part of the sac was rather puffy and investigation as to the reason for same showed it to be the unfolded right broad ligament. In order to be able to ligate the sac properly, it was necessary to get behind the broad ligament, and, when this was accomplished there was seen on its posterior surface a cord-like structure which was recognized to be the ureter. It was carefully dissected off and replaced into the retroperitoneal tissues. The

rest of the operation was presumably of no importance, as it made no lasting impression upon me.

CASE III.—Phillip S., fifty-four years of age, a potential diabetic, was referred to me by Dr. S. Bernstein for the cure of a hernia in the right groin. The physical examination revealed a rather obese individual suffering from a right oblique inguinal hernia the size of a grapefruit, which began fourteen years ago and for which no adequate support was ever worn; in addition to the above, there was also found a left-sided direct inguinal hernia about the size of a hen's egg. I suggested that the large right-sided hernia be operated upon first and if, at the termination of this operation, the condition of the patient warranted it, to proceed with the operation upon the left side. The operation was carried out in general anæsthesia, October 22, 1931, and proceeded perfectly smoothly up to the separation of the sac, except that a large piece of the omentum had to be resected. When the sac was being peeled off, there was noted upon its posterior surface a cord-like structure which was entirely different both in shape, structure and position from the vas deferens and obliterated hypogastric artery and incidentally, I may mention that both these structures were subsequently isolated and recognized as such. The cord, I should say, was not quite round but somewhat ovoid in shape and about one-fourth of an inch in diameter; its outer coat was made up of what appeared to be smooth muscle fibres of a pinkish color. After complete isolation of the sac, the cord was seen to emerge from the internal inguinal ring, descend upon the posterior surface of the hernial sac, make a loop or curve near the fundus, then ascend again upon the posterior surface of the sac, return to the internal inguinal ring where it was lost to sight. It was recognized immediately to be ureter and demonstrated to one of the visiting surgeons, who happened to be present, and several assistants. It was then dissected very carefully from the sac and replaced into the retroperitoneal tissues. Owing to the length of the section of the prolapsed ureter, this was a rather difficult maneuvre but was finally accomplished, I confess, in a rather haphazard manner and only with the aid of Trendelenburg's posture. From this point onward, the operation did not differ from any ordinary uncomplicated hernia. When the patient was returned to his room, the foot of the bed was elevated extremely; I hoped by this maneuvre to elevate the kidney and thereby straighten out the ureter. It is rather difficult to estimate of how much benefit this maneuvre was—suffice it to say, however, that the patient made an excellent recovery without any complications as to kidney function or kidney drainage. When the patient was convalescent, I made an attempt to outline the ureter by an intravenous administration of iopax, but it was not satisfactory and because of the recent operation I did not wish to subject the patient to a cystoscopy. The patient was discharged well November 8, 1931.

This article was already finished and in manuscript when I encountered the following case:

CASE IV.—Miss S. S., sixty years of age, had never been ill prior to her present illness. Twenty-four hours before I saw her, she complained of cramp-like pains in the abdomen and inability to move her bowels or pass flatus; both of these symptoms, however, soon corrected themselves. In spite of this apparent improvement, she consulted her physician and was well enough to visit him at his office, where I also was invited to see her about 1 P.M. April 17, 1932. My examination revealed a somewhat tender right-sided femoral hernia. Her general and local condition, however, were excellent and as her bowels had moved very freely, I made the diagnosis of a strangulated femoral hernia and unhesitatingly stated that most probably, the contents were a bit of omentum and in consequence, postponed operation until the following day. My surprise and chagrin may therefore be imagined when I found that the presumed bit of omentum turned out to be not omentum but strangulated small intestine in the form of a Richter hernia, fortunately in a viable condition. A further complication was the following:

When the sac was pulled up into the inguinal region from its femoral location, as I am accustomed to doing in all operations for femoral hernia, I proceeded to clear the sac of all extraneous tissues and had already transfixed it preparatory to ligation when I noticed on its outer and posterior surface a somewhat ovoid cord-like structure which did not belong there. I proceeded to investigate this cord and found that it made its exit from the retroperitoneal space, then descended upon the postero-external surface of the sac for a short distance, then turned mesially and was lost in the juxtavesical fat which was present and recognized as such prior to the discovery of the ureter. The cord-like structure could only be either the ureter, the round ligament or the tube; only the ureter came into consideration, however, as all the other structures were identified. The ureter was carefully dissected off the peritoneum, a not at all easy matter owing to its dense adherence to the latter; when liberated, it was about three inches long. It was replaced into the retroperitoneal space and the operation finished in the usual manner. At date of this writing, patient is still in the hospital but has made an excellent and uncomplicated recovery.

The four cases cited above bring up the total number of cases of hernia of the ureter to approximately fifty-one. It exists in both sexes and may be of the inguinal or femoral variety.

I have been much interested throughout my entire career in what may be termed abnormal herniæ, but which I prefer to call hernia out of the ordinary. Hernia of the ureter is not only out of the ordinary, but is so extraordinary that its very existence has been denied by outstanding surgeons. My own cases as well as the sparse cases reported by very excellent observers not only prove their existence, but to my mind, warrant this publication.

Discussion.—Dr. Howard Lilienthal (New York City) believed that it would have been a simple matter to catheterize the ureter through the bladder, and also, that methylene blue might be injected through a fine needle passed obliquely through the urethral wall into the ureter and that the dye could then be easily and immediately recognized in the urine.

Dr. Arthur D. Bevan (Chicago, Ill.) asked whether any of these cases were associated with sliding hernia of the bladder or were they entirely independent of such condition.

Doctor Moschcowitz.—Some of the cases of uretral hernia reported were associated with a sliding hernia of the bladder, others were not.

THE SURGICAL TREATMENT OF HÆMORRHAGIC DUODENAL ULCER

By Donald C. Balfour, M.D.
of Rochester, Minn.

Hæmorrhage is one of the major complications of peptic ulcer. Its occurrence is serious, not as a cause of death, since it is rarely fatal, but because of the disability associated with a massive hæmorrhage, the uncertainty as to outcome and the fact that the patient believes that recurrence of the hæmorrhage should be preventable. Hæmorrhage from a peptic ulcer, therefore, though not a great menace to the life of the patient, is certainly a menace to his health and to his peace of mind. Since hæmorrhage from a duodenal ulcer presents problems which are not encountered from bleeding associated with gastric ulcer, I shall confine this consideration to hæmorrhagic duodenal ulcer.

It is difficult to determine the liability of hæmorrhage from duodenal ulcer. Although in about 20 per cent. of cases coming to operation for duodenal ulcer a history of hæmorrhage is obtained, this does not represent the true incidence of the complication since it may occur in cases in which operation is not performed and the patients may be entirely unaware that bleeding has taken place. In consecutive cases in the clinic, in which the diagnosis was duodenal ulcer, a history of definite hæmorrhage is given in about 10 per cent., but if the course of the disease in the non-surgical case is followed over a period of ten years after the positive diagnosis is made, the incidence will be increased to about 25 per cent. This also does not represent the total liability, since it is not uncommon for the complication to occur at a period later than ten years.

The significance of a gastro-intestinal hæmorrhage occasionally presents a difficult problem. In a case of proved duodenal ulcer it may reasonably be assumed that a frank hæmorrhage is due to the ulcer, but it is well to keep in mind that other factors may exist which directly or indirectly are responsible. One of the causes of disappointing results following surgical treatment of duodenal ulcer in a case in which one or more hæmorrhages have occurred, is the overlooking of these other factors; for instance, lesions of the spleen, liver, small intestines, or chronic infections.

The most difficult group of cases is that in which hæmorrhage occurs without previous symptoms of ulcer, and in which exhaustive clinical and röntgenological examination subsequent to the bleeding fails to disclose a lesion. In such cases the hæmorrhage is usually due to an inflammatory process in the duodenum which is not sufficient to disturb gastric function and produce symptoms, or to give direct or indirect evidence of its presence by röntgenological examination. Such cases are puzzling, but fortunately

they are relatively rare, and if the hæmorrhage is repeated, the cause usually becomes evident in the positive data afforded by röntgenological examination.

The mechanism of hæmorrhage is not clearly understood. It cannot be explained satisfactorily, for example, why massive bleeding occurs from a duodenum which shows little, if any, ulceration of the mucosa. Mann's explanation that it is due to the traumatizing of granulating buds in the base of a healing ulcer would seem most reasonable for the majority of cases of actual ulceration. The more rare hæmorrhage, due to erosion of an artery, is easily understood.

In the absence of sufficient ulceration to explain the hæmorrhage, the rôle of the liver must be considered. W. J. Mayo has always strongly emphasized the importance of eliminating all possible factors when recurrence takes place in cases in which there does not appear to be sufficient pathological change in the duodenum to account for the attacks. It is quite possible that the same infection which exists in the duodenum has involved the liver and set up cirrhotic changes, as Rolleston pointed out and described as latent cirrhosis. It is important, therefore, to use every means to determine by tests of hepatic function whether the liver is involved.

Similarly, every method of detecting splenic enlargement, especially by röntgenology, should be employed. In some cases, the explanation of persistently recurring hæmorrhages is obscure and disturbance of the portal circulation offers the most plausible reason. It is significant clinically that hæmorrhages which the inflammatory condition of the duodenum does not fully explain are not fatal, whereas those which are fatal can be shown to be due to erosion of a large vessel in the base of the ulcer.

Differential diagnosis must further exclude other extraduodenal lesions within the abdomen. The most definite of these are lesions of the small intestine (tumors, ulcerations or Meckel's diverticulum with aberrant gastric glandular tissue in its wall), appendix, and so forth. Such lesions are so well concealed that repeated operations may be carried out without avail for a duodenal ulcer erroneously supposed to be responsible for the bleeding. It is, therefore, imperative in operating for hæmorrhagic duodenal ulcer to recognize that some other lesion within the abdomen may be a factor, or possibly the only factor, responsible. This is particularly true in cases in which failure to control the bleeding has followed operation for the duodenal ulcer. This fact should not be emphasized beyond the point, however, that by far the most common cause of hæmorrhage is duodenal ulceration.

The treatment of acute hæmorrhage at present is usually non-surgical, since patients generally recover without operation. I believe, however, in exceptional cases when the bleeding continues and the presence of an ulcer is known, that massive transfusion of blood, followed immediately by a direct surgical attack on the ulcer, is sound treatment. It is an interesting fact that the greater the experience of the surgeon in this field of surgery, the more likely will he consider the advisability of operation in certain acute cases. The situation parallels that of pulmonary embolism, in which embolectomy

becomes justifiable if the patient is obviously dying. If, in spite of repeated transfusions, circulation cannot be maintained, operation could be looked on as justifiable and should consist of a direct attack on the ulcer, either by excision or by suture.

The surgical treatment of the hæmorrhagic duodenal ulcer is the chief purpose of this paper. The indications for operative measures are clear when frank hæmorrhage has occurred in a case of chronic duodenal ulcer, the symptoms of which have been inadequately controlled. A massive hæmorrhage apparently threatening the life of the patient justifies operation even if other symptoms are slight or absent. Recurring hæmorrhage with intervals of complete freedom of all symptoms and complications for varying periods is adequate reason for operation.

A single hæmorrhage of moderate severity, if the patient suffers little inconvenience from the ulcer, is not sufficient grounds for advising operation. A difficult problem is presented by the patient with recurring hæmorrhages, the cause of which cannot be definitely established because of the absence of other symptoms and because röntgenological studies of the gastrointestinal tract are either negative or inconclusive. Exploration should be advised in such cases and a lesion of the duodenum will probably be discovered, usually of the posterior wall, and more distant from the pylorus than such lesions commonly occur. Although it is apparently true that a slight inflammatory process without actual ulceration in the duodenum may be responsible for a single hæmorrhage, and also be difficult to detect at operation, it is also true that recurrences due to lesions in the duodenum are dependent on real ulceration, often completely concealed until the duodenum is widely opened.

The successful surgical treatment of hæmorrhagic duodenal ulcer demands familiarity with various surgical procedures, their indications and their proper performance. Gastroenterostomy can be fairly placed first in importance, because of its safety, its applicability to all cases and its efficiency in bringing about healing of the lesion, or lesions, in the duodenum. These facts give it very distinct advantages over all other operations. A review of the results of gastroenterostomy (posterior or anterior) for hæmorrhagic duodenal ulcer five years or more after operation shows that 85 per cent. of the patients have had no further hæmorrhages and have had no further symptoms of ulcer; such results frequently deter the surgeon from attempting operations more radical in principle and consequently of greater risk. There are two main disadvantages to gastroenterostomy. First, it may fail to prevent reactivation of the inflammatory process in the duodenum—I believe this is extremely rare if the gastroenterostomy has been properly performed and continues to function well. Secondly, recurrence of ulceration may take place in the jejunum. This complication occurred in about 4 per cent. of the cases in which gastroenterostomy alone had been done for hæmorrhagic duodenal ulcer during a period of five years or more after operation. It is of interest to note in such cases that recurrent jejunal ulcer is usually of the bleeding type and this adds to the probability that

there is an abnormal tendency to bleed in certain cases of ulcer. Recurrent jejunal ulcer does not present as serious a problem as one might be led to believe for the simple reason that there is little risk in disconnecting the gastroenterostomy and a method of treatment which has probably brought about complete healing of the primary lesion has been discontinued. It is usually advisable, however, in such cases, also to excise or resect the healed area in the duodenum by whatever method seems best under the circumstances.

The principle of direct attack on the hæmorrhagic duodenal ulcer is logical. The advantages of thorough removal of the lesion combined with a procedure which will prevent its recurrence are obvious. Theoretically and in actual fact, complete excision of the ulcer combined with gastroenterostomy satisfies both requirements, and when this can be done without introducing a too mutilating and, therefore, dangerous technical procedure on the duodenum, it becomes a most efficient method of treatment. The obstacles to such treatment are usually technical, because of the situation of the lesion, the obesity of the patient, or the fixation of the duodenum. Even if direct attack is interfered with by such conditions, partial removal with deep sutures carefully placed on the vessels of the gastrohepatic omentum leading to the site of the ulcer are useful. Cautery excision followed by suture can be satisfactorily employed as a quick and efficient method of handling lesions on the anterior wall in particular. For lesions on the posterior wall awkwardly situated it possesses definite advantages over other methods of excision. Direct excision also usually permits satisfactory inspection of the entire first segment of the duodenum, and the information thus acquired is of the greatest importance in solving the problem as to the most efficient treatment.

Another general principle of surgical treatment of hæmorrhagic duodenal ulcer is excision followed by reconstruction of the pyloric outlet. Such treatment is based on sound surgical principles, since in carefully selected cases it fulfills the major requirements of removal of the lesion, adequate modification of gastric physiology and minimal risk. The advantage of a thorough inspection of all of the first part of the duodenum is more positive with this type of operation, since with the wide removal of the anterior half of the pyloric muscle and the adjacent portions of anterior wall of stomach and duodenum excellent exposure of the posterior wall of the duodenum is possible. The second advantage, namely, the elimination of the factor of pylorospasm, in many cases at least, is of the greatest importance since it accomplishes in them control of the disease. The risk of the operation, when cases are carefully selected, is less than any other procedure. In the last 400 operations of this type, the mortality rate was .27 per cent. The protection against further hæmorrhage was at least 70 per cent. and in cases in which recurrence does take place a different type of operation easily can be done and usually is followed by good results.

The principle of duodenal exclusion is one which merits attention, because inflammatory processes in the duodenum when completely excluded from all gastric secretion are almost certain to heal and remain healed. In

the earlier application of this principle, as by the method of von Eiselsberg, of dividing the pylorus, the disappointing results were due to the high liability to jejunal ulcer because of the secretory products of the entire stomach being diverted into the jejunum. Devine modified this procedure by dividing the stomach well above the incisura, closing the lower segment and restoring gastro-intestinal continuity by some form of gastrojejunostomy. Insufficient data concerning late results necessitate reservation of opinion as to its efficacy in preventing the development of jejunal ulceration, but it is most efficient in promoting healing of the primary lesion. Finsterer, in certain cases, employs the principle but adds removal of the pyloric antrum on the assumption that the antrum is a factor in promoting the secretion from the acid cells of the fundus. I believe the operation is one which should be included in the list of useful procedures for hæmorrhagic duodenal ulcer.

The most thorough treatment for hæmorrhagic duodenal ulcer is partial duodenectomy combined with gastric resection. Such a procedure satisfies best the requirements for good ultimate results in that it removes the vulnerable portion of the duodenum and brings about such a profound change in gastric physiology that those factors, mechanical and chemical, which were chiefly responsible for the ulceration are more or less completely and permanently controlled. In this respect the operation is not equalled by any other procedure. The operation, however, has the very unfortunate disadvantage of being of much greater risk than any of the other procedures, a disadvantage made greater by the fact that the conservative procedures will bring about the same results in a high percentage of cases. I am convinced, however, that since partial duodenectomy and gastric resection reduces to a minimum the recurrence of ulceration that it should be employed when it can be done without greater risk than more conservative measures. This requires experience, judgment and a reasonably accessible duodenum. The method of restoring continuity will vary with the condition of the duodenal stump. Billroth No. I is, I believe, preferable when it is feasible; in some cases after the method of Finney and von Haberer. In cases in which such anastomosis is impractical, a hook-up of fundus and jejunum by one of the many methods is indicated. It is true that such an operation does not absolutely insure against recurrence. I have, within the month, operated upon two physicians with recurrent bleeding jejunal ulcers following gastric resection for hæmorrhagic duodenal ulcer. It so happened that in both these cases the recurrence apparently could be at least partly attributed to too little resection. A very useful surgical procedure for recurrence which takes place under these circumstances is resection of the jejunum, end-to-end jejunojejunostomy, reresection of the stomach and reimplantation of the stomach into the second portion of the duodenum.

The surgical treatment of hæmorrhagic duodenal ulcer is a difficult problem and disappointing results may follow any procedure. An attempt to establish a routine method of treatment increases morbidity and mortality, and as it is true in uncomplicated duodenal ulcer, it is even more true in

ulcer complicated by hæmorrhage that careful selection of the operation best suited to all the conditions met in the individual case is the best form of treatment. The importance of being certain that the sole cause of the hæmorrhage is in the duodenum, and the low operative mortality rate of effective conservative procedures, cannot be overemphasized.

DISCUSSION.—DR. GEORGE W. CRILE (Cleveland, Ohio) discussed the biological method of producing an arrest of hæmorrhage which is based upon the work of Doctor Cannon, who showed that in the presence of a hæmorrhage of considerable proportion, there is excited an increased output of adrenaline and the effect of adrenaline is that of promoting clotting. Upon this point of view Doctor Crile initiated a method to be used in case of internal hæmorrhage from a duodenal ulcer or any other cause. The surgeon himself sits by the bedside, putting a light tourniquet on each thigh, applying just sufficient pressure to prevent the flow of blood from accumulating in the extremities, and has the patient propped up on a pillow until the patient is about to faint. The fainting, the last ditching in before death, will arrest hæmorrhage, and principally because it excites an increased flow of adrenaline. The surgeon sits by the bedside watching the patient's condition and allowing him to go on bleeding until the condition of a moderate fainting is induced. Then the patient is allowed to lie down and first one then the other tourniquet is released so that the blood comes back to the extremities gradually.

It nearly always happens that a hæmorrhage can be arrested by this process.

DR. LINCOLN DAVIS (Boston, Mass.) spoke of that aspect of bleeding duodenal ulcers that Doctor Balfour mentioned in which he understood him to say that he thought where there was an erosion of the gastroduodenal artery, little could be done.

The speaker had had very unfortunate experiences with three such cases. In one case there was a massive sudden hæmorrhage in a strong, robust Negro, which exsanguinated him; after a transfusion he was operated upon and the ulcer was approached by opening the duodenum and, when a clot was washed away, there was a terrific hæmorrhage from the base of the ulcer which was controlled only by placing the finger over the ulceration. It was a very difficult situation. The cautery was evidently out of the question. An attempt was made to put sutures across the floor of the ulcer and control the bleeding. Eventually the bleeding was stopped, but the outcome was unsuccessful.

A short time after that they had another case of the same type, a very sudden, terrific hæmorrhage in which there had been some evidence that the man had a duodenal ulcer. In this case, at the suggestion of Dr. D. F. Jones, he approached the ulcer in a different way, transecting the duodenum at the pylorus and turning the duodenum back and then tying off the gastroduodenal artery above and below and doing a Billroth I operation.

That patient also succumbed. He was in desperate condition and though he was transfused, he wasn't able to rally. Post-mortem examination showed an erosion of the gastroduodenal artery, that artery will bleed as freely as the radial.

A third case was not operated on at all. He had a massive hæmorrhage in the medical ward and was transfused two or three times, but he died and an autopsy showed another one of these eroding ulcers which had eaten through the wall of the gastroduodenal artery.

DR. F. N. G. STARR (Toronto) said, apropos of Doctor Crile's remark, it may perhaps be interesting to know that forty-odd years ago as a student in the office of the late Dr. W. T. Aikins, of Toronto, when he was approaching an operation in which there would likely be a good deal of shock or a considerable hæmorrhage, he invariably put a tourniquet on each arm and each leg and then when the operation was finished—and I may say during many of these there wasn't anything like the amount of bleeding that

was anticipated—and the dressing on, then the job was very gently to take off one tourniquet from the arm, the other from the other arm, one from the leg, and so forth.

Speaking of the bleeding duodenal ulcer, he thought Doctor Balfour had sounded a very good note in the endeavor to do the simplest types of operation that will cure. He had had the experience on several occasions of a patient coming in as a result of a serious hæmorrhage. Transfusion bucked them up and the patient was pretty well for two or three days. Then he noticed him getting pale and, doing a hemoglobin, it was found to be down again. He was transfused again, and again he improved, but the bleeding proceeded and there was still melæna in his stools; then operation seemed imperative.

Upon opening the duodenum, he found a posterior duodenal ulcer which was spurting a tiny little stream in very tiny jets. The ulcer was either excised or cauterized and then oversewn, and afterward there was ligation of the gastroduodenal artery followed by a gastroenterostomy.

Dr. John H. Gibbon (Philadelphia) spoke about transfusions in the presence of, or following, profuse gastric hæmorrhage. He was convinced, with the intravenous method as at present employed, and with transfusions of large amounts of blood, that the mortality in gastric hæmorrhage has been very much increased. If transfusion is used at all, only very small amounts of blood should be given.

He had seen two or three patients who represented a course very much like that described by Doctor Starr. After each transfusion there was a temporary buck-up followed by another hæmorrhage. One of these patients made a very rapid recovery when transfusions were stopped and fluids given only under the skin and by the rectum.

Dr. Francis A. Scrimger (Montreal) recounted a recent instance where a man came in with a sudden large hæmorrhage and vomited some 500 or 600 cubic centimetres of blood, in addition to blood from the bowels, in which the red cells went down to less than a million, in which there was difficulty in breathing, in which he had reached the point of fainting, and in which a small transfusion was given which improved him.

I may state in our experience these small transfusions of not more than 300 cubic centimetres of blood have not raised the blood-pressure appreciably, not more than above 4 or 5 per cent.

This man, whether on account of the blood transfusion or in spite of it, bled again another 500 cubic centimetres. He was again transfused and immediately operated upon. Just at the turn of the duodenum, there was a large bulge, almost like a diverticulum. In this was the ulcer on the upper surface, very much inflamed and attached to the pancreas. In that diverticulum was seen projecting a vessel quite as large as the lead of a pencil, which was actually bleeding at the time of the opening. Possibly the trauma had started it again.

The vessel was ligated and the ulcer obliterated by sutures. It had already been entirely denuded of mucosa.

Dr. Donald C. Balfour (Rochester, Minn.) thought the cases Doctor Davis had described to be extraordinary and yet he believed that the patient in such circumstances usually has to fight it alone—except for transfusions. At the same time, he said, one could have the impression that the bleeding vessel might be reached by operation and ligated or sutured. It is indeed fortunate, however, that the patients usually recover without operation.

The question Doctor Starr brought up, of operating on the patient who continues to bleed in spite of transfusion, is most important and there will be general approval of that method. If a patient steadily goes downhill with each hæmorrhage, we give a transfusion and open up widely to see what can be done, because the risk of operation under those circumstances is less than the risk of a patient's carrying on himself.

He agreed with Doctor Gibbon on the danger of transfusion, particularly massive transfusion in these patients. Such are ill advised, and the practice at Rochester is not to do it until a patient is apparently dying and then a small transfusion is given; repeated if necessary to carry the patient along.

CARCINOMA OF THE STOMACH—AN ANALYTICAL SURVEY

By Gatewood Gatewood, M.D.
of Chicago, Ill.

The fatalistic attitude common among physicians and patients has led me to make a survey of our carcinoma cases in the hope of discovering some remedial shortcomings and of improving our future results. Carcinoma of the stomach continues to lead the list of deaths from malignancy, the figures varying from 35 to 40 per cent. in the statistics of the various countries of the world.

In 1930, I reviewed the results of resection for gastric malignancy in patients operated upon during the preceding decade.[1] This survey includes *all* patients who entered the Presbyterian Hospital between January 1, 1920, and December 31, 1929, in whom the diagnosis of carcinoma of the stomach was made. Of these 417 patients, 209, or exactly 50 per cent., were discharged without operation for the following reasons:

Carcinoma of the cardia	30 or 14.4%
Previously operated upon*	17 or 8.1%
Too extensive (evidence of metastases, ascites, etc.)	46 or 22 %
Too sick for operation	27 or 17.7%
Cause not stated (most of these were extensive carcinomas)	50 or 23.9%
Refused operation (considered operable)	24 or 11.5%
Went elsewhere for operation	5 or 2.4%

* Of the seventeen patients who returned after operations done prior to 1920, or done elsewhere, eleven had had resections and six gastroenterostomies.

The operative cases have been grouped as explorations, gastroenterostomies, resections and palliations such as gastrostomy or enterostomy. Although a slightly larger proportion of patients has come to operation during the past three years, there still were 45 per cent. who were either pronounced inoperable or refused operation.

Analyzing the histories of all of these patients, we find 308 males and 109 females, or a ratio of 2.8 to 1, which is a somewhat higher proportion than is usually found, although Ransom and Coller[2] report that 85 per cent. of the patients in their series were male. The ages varied from twenty-four to eighty-nine years, six being under thirty years of age.

An attempt was made to ascertain how long after the onset of symptoms the patient had consulted a physician, and, where sufficient data were given, the delay averaged 5.3 months (sixty reporting shortly after onset). Nine patients admitted having been treated over considerable periods of time by chiropractors or cultists. It was impossible to ascertain from more than one-third of our histories how much time elapsed between the time the patient first saw a doctor and the date of operation, but the average for each group where sufficient data were given was a little more than eight

months. It was surprising and disappointing to find that this figure did not vary 0.1 month for any group.

Symptoms.—According to the histories, the duration of symptoms varied from a few days to many years. The exact date of onset was indefinite in many cases as patients frequently could not differentiate between chronic bowel disturbances or "indigestion," and the onset of their immediate symptoms. There seem, however, to be two types of history, a short and a long. The short history varies from three years to a few days, and, while the patients have frequently been treated for ulcer, the histories are never altogether typical. Almost 12 per cent. of patients gave a very good ulcer history preceding the present trouble by many years. One of these patients had had a gastroenterostomy done by Doctor Bevan twelve years before, and, at operation, an old healed ulcer was found remote from the site of the cancer. Although there is a great deal of difference of opinion as to the etiological importance of ulcer in cancer of the stomach, a histological study of our resected cases reveals only 6 per cent., which were definitely on an old ulcer base. This is in accord with the figures of Hartmann,[3] Cuneo and Duval, Karsner, and most pathologists.

The most common symptom for the entire group is *pain*, which varied from mild epigastric distress to acute, severe pain. This symptom was complained of in 302 out of 400 (75 per cent.). It was the first symptom complained of by more than one-half the patients. Next in frequency came loss of weight, although only seventeen mentioned it as the first symptom. This weight loss varied from 5 to 115 pounds, the average being most marked in the group of patients who had only exploratory operations, thirty-two pounds, and the least in the resection group, twenty-three pounds. Only four patients in the entire series reported a gain in weight. The next most common symptoms in the order of frequency were vomiting, weakness, loss of appetite, fullness, indigestion, *etc.*, as shown in Table I. It is interesting to note that twenty-seven had definite knowledge of a tumor mass.

The *family history* was negative in the majority of cases, although a definite history of carcinoma in the family was obtained from forty-five patients (11 per cent.). Three brothers in one family died of cancer of the stomach, one patient's father died of carcinoma of the pylorus while his mother had carcinoma of the œsophagus. Were it not for a tendency among medical men in outspoken cancer cases to avoid inquiry into the family history, more carcinoma families might have been discovered.

On examination emaciation was the most common finding although it was entirely absent in 30 per cent. of the resected cases. A definite palpable tumor mass was found 104 times among the unoperated cases (50 per cent.), thirty times among the explorations (62.5 per cent.), fifty times among the gastroenterostomies (67 per cent.), and thirty times in the resections (52 per cent.)—not a great difference. It is my impression that a tumor might have been found in a higher percentage of cases had more of the examinations been made under the fluoroscope, a suspicious sense of resistance often

TABLE I

Order of Complaints

Symptom	1	2	3	4	5	Totals*
Pain	212	41	25	21	5	302
Loss of weight	17	89	89	44	21	282
Vomiting	22	65	34	35	15	177
Weakness	34	35	42	30	18	165
Loss of appetite	25	32	37	14	6	123
Fullness	37	27	14	6	3	90
Indigestion	26	20	5	1	1	56
Anæmia	1	8	5	6	8	50
Tarry stools	1	6	11	4	4	36
Diarrhœa	13	8	6	4	2	35
Difficulty in swallowing	14	7	7	4	1	33
Hæmorrhage	1	6	11	5	6	33
Knowledge of tumor mass	6	6	3	4	5	27
Regurgitation	4	10	4	2	1	21
Jaundice	2	2	1	3	2	11

* The figures in the five columns represent the order in which the patients gave the more common symptoms. The total numbers of *all* patients mentioning the symptoms are listed in the last column. Naturally, many patients had more than five complaints.

becoming definite mass when felt in conjunction with a visible defect. Ascites was found in thirty cases and reported as probable in four others. Virchow's glands were noted in eight cases (2 per cent.). Obviously the presence of Virchow's glands excludes the possibility of radical resection. Although œdema and ascites are usually late, they may result from anæmia and not from implant metastases, as shown in one patient who has been well for five years after resection.

The laboratory findings revealed occult blood in the stools in 95 per cent. of all cases, and in the stomach contents in approximately the same percentage of the cases in which examinations were made. Seventy-three per cent. had no free hydrochloric acid, 16 per cent. had a normal acidity, and the rest were hypoacid. Only one patient had hyperacidity. The percentage of cases with free hydrochloric acid is shown in Table II. It will be noted that the percentage is highest in resected cases, but almost as high in those considered inoperable.

TABLE II

Acidity in Stomach Contents

Type of Operation	Free Acid Present	No Free Acid	Percentage of Cases with Free HCl
Resections	16	35	31.4
Gastroenterostomy	27	45	27.5
Explorations	8	31	20.5
Unoperated	41	99	29.3

Lactic acid was reported as negative in seven of the achlorhydrias, but, according to Dodds and Robertson,[4] this was probably due to inaccurate examination, as they feel that lactic acid is almost always present in the

absence of free hydrochloric acid and show that it is not caused by tumor formation. Polland and Bloomfield[5] believe that the presence or absence of free hydrochloric acid depends upon the amount of gastritis present, bearing out the suggestion of Mathieu, made in 1889. We have made microscopical examinations of remote portions of all of our resected stomachs and have found a certain amount of gastritis almost invariably present. The degree did not seem to bear any relationship to the presence or absence of hydrochloric acid. Comparing cases with obstruction with those which had none, retention of gastric contents did not seem to influence the acidity. Although the presence of pus- and tumor-cells is of diagnostic importance and should always be searched for as well as long bacilli, they were reported in a very small percentage of this series.

The importance of X-ray examination cannot be over-emphasized, the accuracy of diagnosis in all except the occasional ulcer-carcinoma being nearly 100 per cent. The ability of the X-ray department to determine operability is not quite so good and whenever there is a question of doubt, the patient should be given the benefit of exploration. At least three of the fifty-eight resections were thought to be non-resectable on X-ray examination.

The *operative treatment* consisted in the procedures shown in Table III.

TABLE III

Types of Operation

Operations	Male	Female	Total	Per Cent.	Hospital Mortality (Per Cent.)
Explorations	32	16	48	23	32.6
Gastroenterostomies	68	17	85	40.9	25.9
Resections	45	13	58	27.8	32.6
Gastrostomies and jejunostomies	8	7	15	7.2	80
Ileosigmoidostomy	1		1	.5	100
Closure of perforation	1		1	.5	100
Totals	155	53	208	100	

The hospital mortality has been unusually high, but it should be noted that some of these patients remained in the hospital for several weeks after operation. The hospital mortality from gastroenterostomy is almost as high as from resection. Anterior gastroenterostomy with or without enteroanastomosis was made in thirty-six cases and posterior gastroenterostomy was made in forty-nine.

The Billroth II, or some type of end-to-side anastomosis, as the Balfour, or Polya, has been used in all of the resections except one in which the Billroth I was performed. Most of the lesions were extensive, making resection of the colon necessary in one case and part of the pancreas in three. Palliative operations of this type carry a high mortality but one of these patients is well almost ten years later and several palliative resections lived more than three years.

Post-operative Results.—The follow-up of this series has been exceptionally difficult as many of these patients have been dead over eight years, but the diligent efforts of my secretary and myself have been rewarded by reports upon 100 per cent. of the resections, 98 per cent. of the gastroenterostomies and 95 per cent. of the explorations. All of the patients who were explored or upon whom gastroenterostomy was performed are dead. The average length of life following exploration was 6.1 months. After gastroenterostomy, patients lived an average of 8.75 months, or only 2.65 months longer. Following resection, the patients who left the hospital have lived an average of four years and nine months. Those who are alive have lived an average of six and one-half years. The following table reveals that 46.1 per cent. lived over three years, and 36 per cent. are alive at the end of five years, one patient having just passed the twelve-year mark. Four patients died of intercurrent disease, one five years later following cholecystectomy, with no evidence of metastases at autopsy; one, one year later, of a perinephritic abscess without evidence of recurrence (autopsy); one, following prostatectomy four years later (no history of recurrence, but no autopsy); and one of cerebral hæmorrhage which may have been the result of a brain metastasis (no autopsy). (Table IV.)

TABLE IV

Post-Operative Statistics in Gastric Resections for Carcinoma from January 1, 1920, to December 31, 1929

		Subsequent Deaths			Living		
Type of Carcinoma	Total Cases	Under 3 yrs. (in mos.)	3–5 yrs.	5 yrs. plus	Under 3 yrs.	3–5 yrs.	5 yrs. plus
Adeno-carcinoma	22	16, 16, 12, 23, 32, 12, 6, 17, 30*		5 5 and 2 mos.†	2 and 10 mos.		8, 5, 10, 12
Papillary adeno-carcinoma	9	4, 12‡		8½			7, 8
Adeno-scirrhus	6	3	4§		2½	3 and 8 mos.	
Scirrhus	15	15, 28, 19, 19, 7	4	5½ 6 and 2 mos.			
Colloid	2	18				4½	
Ulcer-carcinoma	3			5			9, 5
Linitis plastica	1	24					
Totals	58	19	2	6	2	2	8

* Influenza.
† Cholecystectomy.
‡ Perinephritic abscess.
§ Prostatectomy.

It has been impossible to correlate the pathological findings with the ultimate results except in a general way. The prognosis was worst in the

scirrhus type of lesion, which agrees with the findings of M. Persson[6] and others. It is better in the adeno-carcinoma and, as one might expect, best in the carcinoma on an ulcer base. Some of the more extensive adeno-carcinomas (with glandular metastases) have been symptom-free more than five years.

SUMMARY

Four hundred and seventeen patients with carcinoma of the stomach were admitted to the Presbyterian Hospital between January 1, 1920, and December 31, 1929.

Fifty per cent. of these patients were diagnosed as inoperable at time of admission to the hospital.

Of the operations performed, 23 per cent. were exploratory only, 7 per cent. were palliative for relief of starvation (gastrostomy and jejunostomy), 41 per cent. were gastroenterostomies and 28 per cent. were gastric resections.

The hospital mortality for gastroenterostomy was 26 per cent., and for gastric resections was 32.6 per cent.

A careful follow-up has given the ultimate results in 95 per cent. of exploratory operations, 98 per cent. of gastroenterostomies and 100 per cent. of the gastric resections. The average post-operative length of life after exploration was found to be 6.1 months, after gastroenterostomy, 8.75 months, after resection four years and nine months. The patients living at the present time have survived an average of six and one-half years. After resection 46 per cent. of the patients leaving the hospital lived three years or more. Thirty-six per cent. survived over five years, but of these, five subsequently died of carcinoma. Five patients are living eight or more years after resection, and a few have died without evidence of recurrence.

Free hydrochloric acid was present in 20 to 30 per cent. of cases, without striking difference between the operable and inoperable cases. Diffuse gastritis is present in most cases and does not seem to explain the achlorhydria.

More than a year elapsed between the first symptom and operation in many of the operated cases in this series. If we are to improve our outlook in this important group of cases, barring the discovery of some real cancer cure, our attention must be directed toward earlier diagnosis, better preparation and better technic.

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DISCUSSION.—DR. J. SHELTON HORSLEY (Richmond, Va.) remarked upon the excellent statistics of Doctor Gatewood of permanent cures of cancer of the stomach. He had been much impressed by the statistics published by Saltzstein and Sandweiss,

and by Dr. Margaret Warwick a few years ago. These were all from necropsies. Saltzstein and Sandweiss published the results of 365 necropsies in cancer of the stomach in Detroit. In these 365 cases, only 7.7 per cent. had had an excision of the cancer. Doctor Warwick's statistics in Minneapolis showed that in 23 per cent. of the necropsies in cancer of the stomach there were no metastases outside of the stomach. It seems probable that if 23 per cent. of patients dying from cancer of the stomach have the cancer still limited to the stomach, if the patients were operated upon a few months before death the percentage of cases of cancer limited to the stomach would be even larger. Apparently patients with cancer of the stomach are not receiving a fair deal. While a few of this 23 per cent. of the patients who died with cancer limited to the stomach have cancer in the cardiac portion of the stomach which is inaccessible, it is well known that most cancers of the stomach are in the body or the pyloric end.

If the surgeon could only get these cases a little earlier the percentage of cures after resection would undoubtedly be larger, but even with patients in whom the growth appears to be extensive an exploratory operation sometimes shows that the cancer is resectable even though the röntgenological report indicates otherwise. The cancer of the stomach may be of histologically low grade of malignancy, requiring only a slim margin of apparently healthy tissue for a satisfactory resection.

Whenever it is possible to do a partial gastrectomy, it should be done instead of gastroenterostomy. Gastroenterostomy, which merely short-circuits the food and leaves behind a mass of diseased and often necrotic tissue, does but little good. Partial gastrectomy carefully done, possibly under local anæsthesia, followed by a transfusion of blood, should carry but little higher mortality rate than a gastroenterostomy and gives much greater relief, even if it cannot cure.

Dr. Donald C. Balfour (Rochester, Minn.) was in agreement with Doctor Gatewood on various points, especially the symptomatology and variation in the course of the disease. Some slowly develop carcinoma; such as the type of case in which the patient comes with an achlorhydria, anæmia and negative X-ray and as one follows it along one suspects carcinoma, and suddenly the X-ray reports an inoperable cancer of the stomach. It is interesting to think what is going on in these patients with secretory disturbance and anæmia. Looking up our figures on operability we found that 50 per cent. of the patients with cancer of the stomach come to operation and in about one in five of the cases diagnosed is resection possible.

Doctor Horsley emphasized (it cannot be over-emphasized) that X-ray is valuable in spotting a lesion of the stomach, but possibly we depend a little too much on the X-ray as showing the extent of the lesion and what can be done with it in a surgical way. All patients with carcinoma of the stomach should be explored unless metastases or age contra-indicate.

What Doctor Horsley said about extensive resection is true because some of the patients who were cured, where the nodes were not removed, were apparently incurable because of extensive lymph-node involvement.

In cases of cancer of the stomach the family history of cancer was given in 16 per cent.; of gross hæmorrhage in 12 per cent.; of an average value of hemoglobin of 60 per cent.; of obstruction in 30 per cent.; and 50 per cent. had gastric acidity with normal hydrochloric acid or above.

The classification of Doctor Broders in the patients who had ten-year cures shows 55 per cent. of grades I and II; 35 per cent. of grade III; 10 per cent. of grade IV. In all cases of resection the classification was just the reverse in that 20 per cent. were of grade I and II; 35 per cent. of grade III, and 44 per cent. of grade IV.

CALCIUM CARBONATE GALL-STONES AND THEIR EXPERIMENTAL PRODUCTION

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and
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From the Department of Surgery and the Lasker Foundation for Medical Research the University of Chicago

Calcium carbonate as a separate deposit in the lumen of the gall-bladder in the form of either a white stone or paste and casting dense shadows in röntgenograms was reported in eight cases to the American Surgical Association in 1931 by Phemister, Rewbridge and Rudisill. In all instances the cystic duct was obstructed. The obstruction was produced by an ordinary gall-stone of the cholesterol or cholesterol-pigment variety except in one case where it was due to carcinoma. The order of development was as follows: Cholecystitis and cholesterol or cholesterol-pigment stone formation, engagement of a stone in the cystic duct with long-standing obstruction, low-grade chronic inflammation, reduction in the amount of fluid contained in the gall-bladder and deposition of calcium carbonate in it. In long-standing cases the calcium carbonate formed a large, white, soft stone. When ordinary cholesterol-pigment stones were present they were either incorporated within or partially coated by the calcium carbonate. In some cases sufficient calcium carbonate had been deposited on the stone in the cystic duct and particularly on its gall-bladder side to make it recognizable in röntgenograms along with the calcium carbonate deposit in the gall-bladder. The gall-bladders were smaller than normal and cholecystography revealed non-visualization with tetiothalein.

Of forty-eight consecutive cases operated on for gall-stones since that report, eleven, or 22.9 per cent., were found to have obstruction of the cystic duct by a stone. Six of these, or 12½ per cent., had mild chronic cholecystitis with a separate deposit of calcium carbonate in the gall-bladder. In one case the deposit occurred as a mucous suspension, in four as a semi-solid paste and in one as a solid in the form of coarse sand (Kalkgries). The remaining lumen of the gall-bladder was occupied in five cases by a few cubic centimetres of thick mucus. In one case there was a slightly turbid serous fluid which was obtained for chemical analysis. The remaining five cases with cystic-duct obstruction but without calcium carbonate precipitation showed more marked inflammation of the gall-bladder with serous exudation and the ordinary picture of hydrops.

Experimental work is reported in which, after cystic-duct ligation, a pure calcium carbonate deposit was obtained in the lumen of the gall-bladder of the dog and calcareous deposits too small for accurate chemical analysis within the gall-bladders of rabbits.

The six cases are grouped as, first, those in which multiple cholesterol-pigment stones, and second, those in which a single cholesterol stone, in the gall-bladder, preceded the development of cystic-duct obstruction obstruction and the deposition of the calcium carbonate. They are arranged in each group according to the apparent age of the deposit, beginning with the earliest.

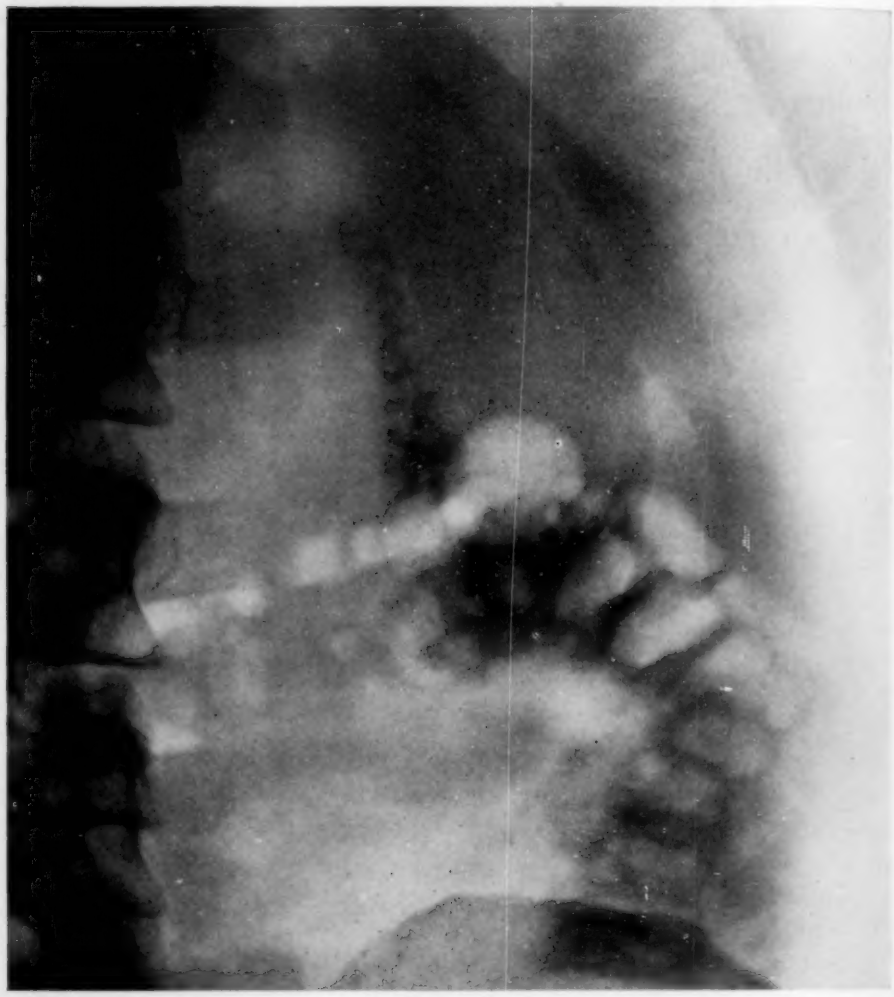

FIG. 1.—(Case I.) Röntgenogram of gall-bladder before tetiothalein administration.

CASE REPORTS

CASE I.—H. F., male, aged forty-five years, had had attacks of gas pains in the abdomen for seventeen years. Appendectomy sixteen years ago with no relief. Loose and frequent stools at intervals. During the past two years has had at irregular intervals attacks of epigastric pain, at times associated with nausea and vomiting, lasting from a few minutes to three or four hours. Has never had fever or jaundice with the attacks. Physical examination revealed a healthy-appearing man and regional examination was essentially negative. A röntgenogram (Fig. 1) showed a radio-opaque shadow

in the gall-bladder region which was smaller and narrower than a normal gall-bladder. Scattered throughout it were numerous radio-translucent areas with ring-shaped densities

FIG. 2.

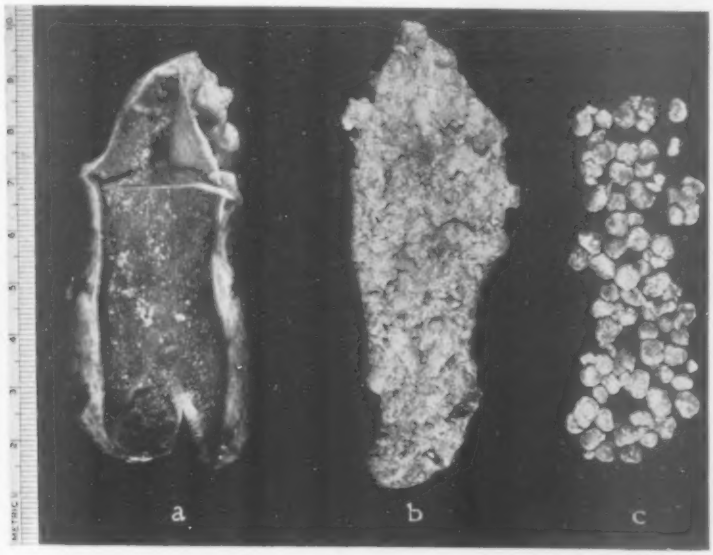

FIG. 3.

FIG. 2.—(Case I.) Röntgenogram of excised gall-bladder.
FIG. 3.—(Case I.) Photograph of (a) gall-bladder; (b) mucus which contained calcium carbonate; (c) gall-stones.

about their periphery. Cholecystography revealed non-visualization of the gall-bladder with dye and no change in the shadow in the gall-bladder region.

Operation revealed a gall-bladder smaller than normal, free from adhesions and

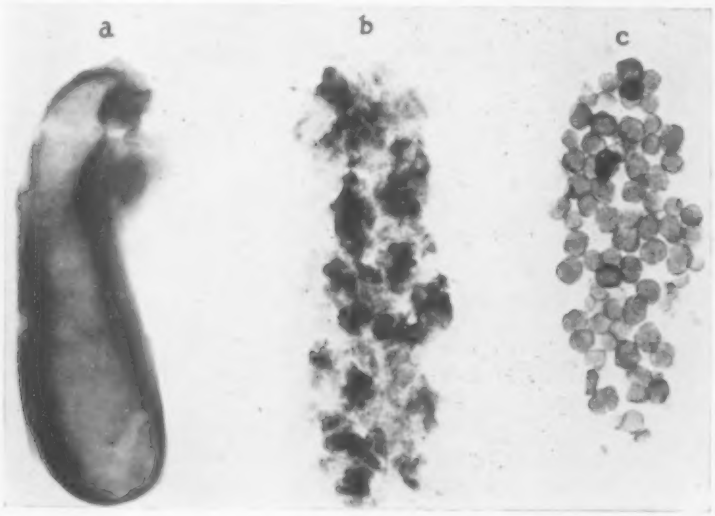

FIG. 4.—(Case I.) Röntgenogram of specimens shown in Fig. 3. (b) Calcium carbonate shadows in the mucus.

containing many stones. There was also a stone in the cystic duct. Cholecystectomy. A röntgenogram of the specimen (Fig. 2) showed numerous radio-translucent shadows, some of which had a narrow rim about their periphery. Between the radio-translucent

areas there are diffuse radio-opaque shadows. Section of the gall-bladder showed it to be filled with a dark green, opaque, thick, mucous fluid containing many spherical stones, and there were two stones in the cystic duct. The gall-bladder wall was slightly thickened and its mucosa appeared to be intact. Fig. 3 shows separately the interior of the gall-bladder, its mucous content, throughout which was distributed a grayish, opaque, soft substance, and the gall-stones. Fig. 4 shows a röntgenogram of these structures. The mucous mass casts a heavy irregular dense shadow and some of the gall-stones

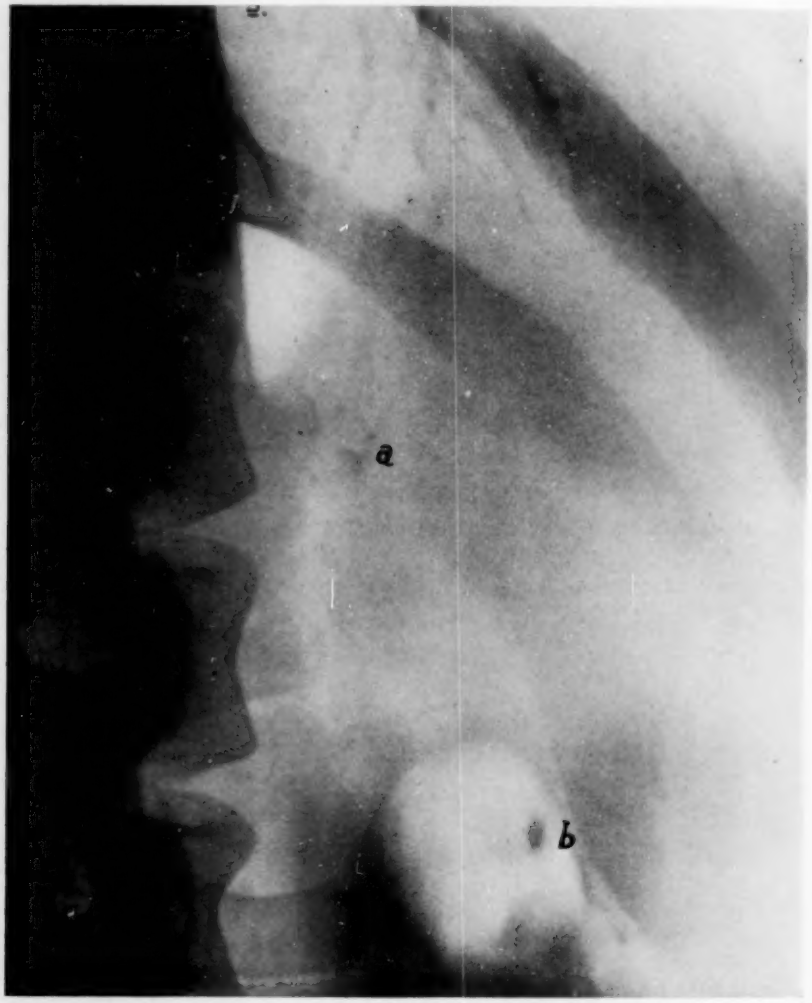

FIG. 5.—(Case II.) Röntgenogram showing shadow in region of cystic duct (a) and gall-bladder (b).

show radio-opaque rings about their surfaces. A chemical analysis of the thick mucous material revealed calcium 14.5 milligrams, phosphorus 1.0 milligrams, and CO_2 14.1 cubic centimetres per 100 milligrams dry exudate. The content was not sufficiently solid for an accurate calculation of the percentages of calcium carbonate and calcium phosphate present. Cholesterol and bile pigment present.

This represents an early stage in deposition of calcium carbonate in the gall-bladder. The mucous was stained with bile which indicated either that the calcium had been deposited before the bile pigments had been absorbed

or that a small amount of bile had continued to enter past the stones in the duct. The calcium had not yet begun to collect into soft solid masses as in the older cases.

Case II.—I. T., male, aged thirty-six years, had had frequent attacks of pain in the right upper quadrant of the abdomen during the past five years, lasting usually for a few hours. They might come as often as twice a week, but might not recur for ten

Fig. 6.

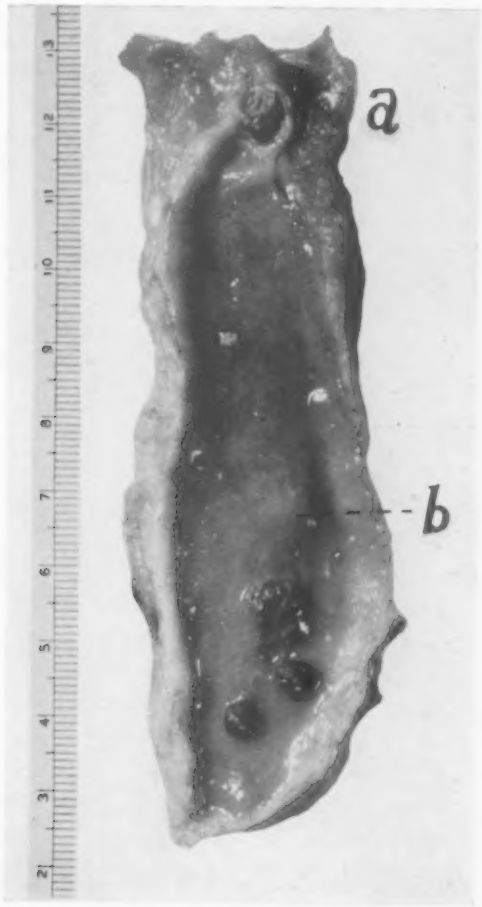

Fig. 7.

Fig. 6.—(Case II.) Röntgenogram of specimen showing shadow of stone in cystic duct (a) and of calcium-carbonate paste (b), as well as ring shadows of calcium on two cholesterol pigment stones.

Fig. 7.—(Case II.) Gall-bladder opened exposing stone in cystic duct (a) and calcium-carbonate paste buried in mucus (b). Cholesterol-pigment stones are distal to it.

weeks, with complete relief during the intervals. Vomiting had been frequent, but the attacks were short and not accompanied by fever or jaundice.

Physical examination revealed a healthy-appearing, well-nourished male. Regional examination essentially negative. No masses nor tenderness in gall-bladder region. A röntgenogram (Fig. 5) revealed two radio-opaque shadows in the right upper quadrant, a small one in the region of the cystic duct and a larger one in the region of the gall-bladder. Cholecystography showed no change in the films taken after intravenous administration of tetiothalein. At operation the gall-bladder was found markedly collapsed, as if it had been emptied by aspiration. There was a stone in the first portion

of the cystic duct and there were small stones in the gall-bladder. Findings were otherwise negative. Cholecystectomy including portion of cystic duct containing stone. A röntgenogram of the specimen (Fig. 6) revealed ring shadows on the stones in the gall-bladder and a ring shadow broadest on the gall-bladder side of the stone in the

FIG. 8.—(Case III.) Gall-bladder shadow before administration of dye.

cystic duct. There was also a separate uniformly dense oval shadow in the gall-bladder.

Pathology.—The gall-bladder (Fig. 7) was nine centimetres long and collapsed. On section its wall was slightly thickened and its lumen contained only a few cubic centimetres of a slightly bile-stained thick mucus in which were three rough brown stones and a grayish white, slimy mass about one centimetre in diameter, of the consist-

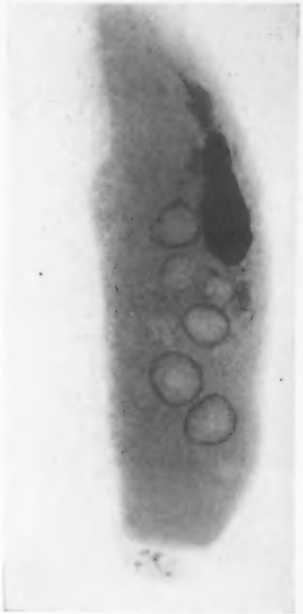

FIG. 9.—(Case III.) Röntgen-gram of specimen showing shadows of ring stones and of calcium carbonate which had changed in shape from that in Fig. 8.

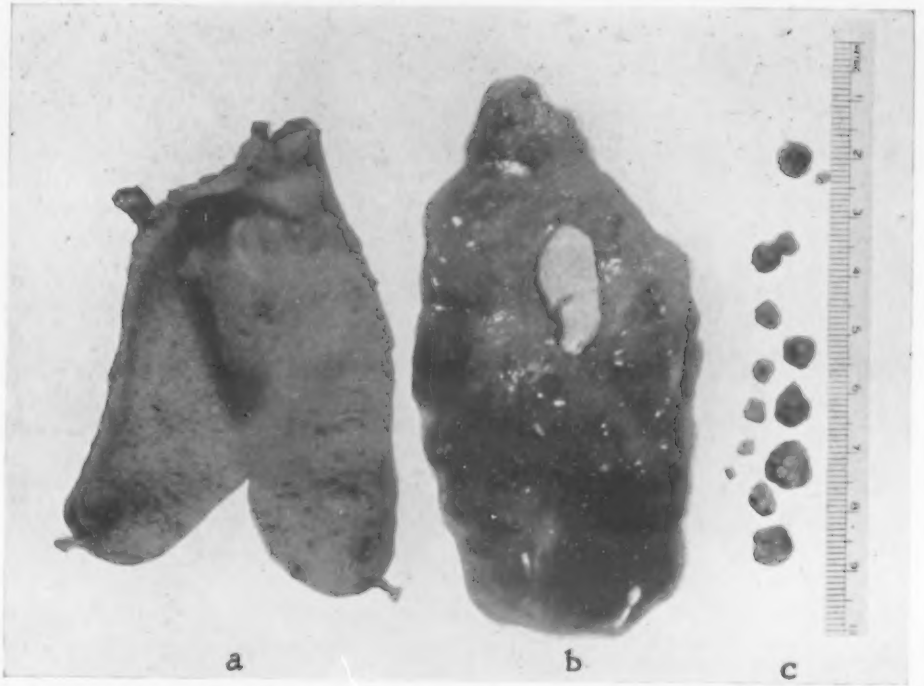

FIG. 10.—(Case III.) Photograph of (a) gall-bladder, (b) mucous content with oval gray mass of calcium-carbonate paste and (c) gall-stones.

ency of paste. A stone was tightly embedded in the cystic duct. It had a lighter brown color on the gall-bladder side than on the side away from it.

Microscopical examination showed mucosa intact and villi crowded together. There was a slight amount of round-cell infiltration of the wall and extremely little fibrosis.

Cultures on Rosenow's media of the mucus and wall remained sterile. Chemical analysis of the paste-like mass gave: calcium carbonate, 64.3 per cent.; calcium phosphate, 0.7 per cent.; the rest was organic matter. Bile pigment was present in the mucus by the nitric-acid test and cholesterol was absent.

The presence of calcium carbonate X-ray densities incorporated in ring form in the periphery of the cholesterol-pigment stones suggests that the calcium carbonate was laid down in the presence of obstruction and the growth of the deposit into a thick layer on the gall-bladder side of the stone in the cystic duct renders this assumption

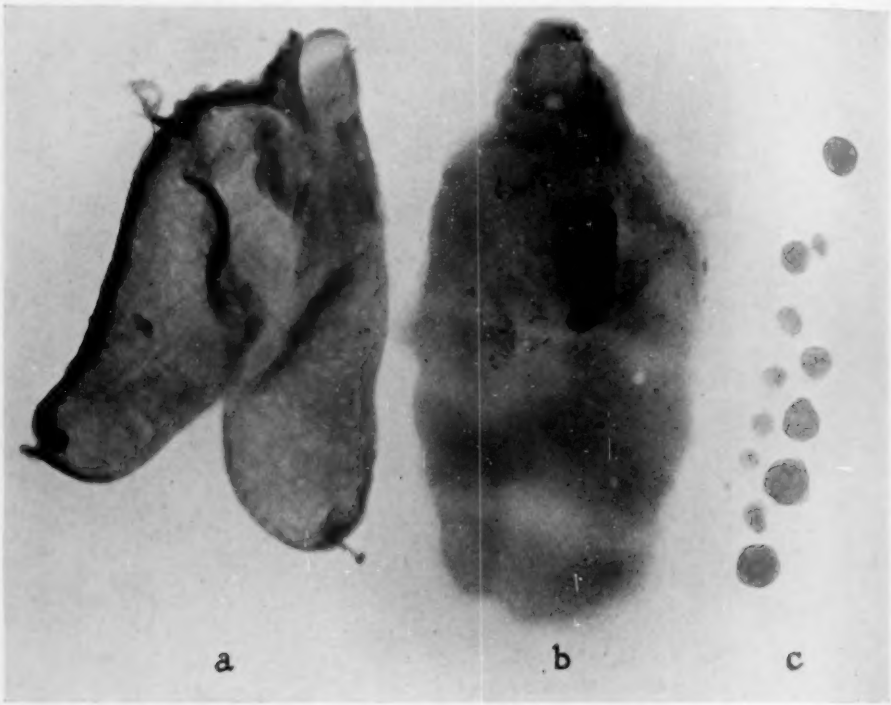

FIG. 11.—(Case III.) Röntgenogram of specimens in Fig. 10; (b) dense shadow of mass of calcium carbonate.

almost a certainty. It is known, as reported by Romang, that the radio-opaque shadows cast by gall-stones are due practically entirely to calcium carbonate, since only small amounts of calcium phosphate are ever present and the calcium-pigment salts contain so little calcium that their radio-opacity is but slightly greater than that of water.

CASE III.—C. O., male, aged sixty-one years, had had attacks of pain in epigastrium and right upper quadrant at irregular intervals for seven years, occasionally associated with nausea and vomiting. Within the past eleven months he had had three attacks that were followed by jaundice. The last one occurred two months ago and slight jaundice lasted for one month. Much epigastric distress during the period. Physical examination was essentially negative aside from increased resistance in gall-bladder region. No jaundice. No bile in urine. Patient brought a röntgenogram taken seven and one-half months previously which revealed a small pear-shaped opaque shadow in gall-bladder region in which were circular radio-translucent shadows. (Fig. 8.) Another radiogram was made which revealed a slightly smaller but more dense, oval,

radio-opaque shadow in the same region. Cholecystography showed no shadow of dye in the gall-bladder region. At operation the gall-bladder was found to be much smaller than normal, and flaccid. Its wall was somewhat thickened and several stones were palpated. A stone was tightly impacted in the cystic duct. Cholecystectomy. A röntgenogram of the gall-bladder (Fig. 9) revealed several radio-translucent circular shadows with dense rings or specks about the periphery. In addition there was an oval radio-opaque shadow two centimetres long and separate radio-opaque flecks in its

FIG. 12.—(Case IV.) Röntgenogram of gall-bladder before tetiothalein administration.

vicinity. On section the gall-bladder contained a thick, light green mucous fluid. Imbedded in it were fourteen mulberry stones of various sizes and grayish to brown in color. There was one oval, paste-like, grayish mass two centimetres in length and numerous grayish flecks seen in the mucus. (Fig. 10.) A röntgenogram of the gall-bladder, mucous content and stones (Fig. 11) shows faint rings about some of the gall-stones and a dense radio-opaque shadow cast by the paste in the mucus. Cultures on blood agar plates and Rosenow's media remained sterile. Microscopical examination of the gall-bladder revealed a small amount of fibrosis and moderate infiltration of the wall with lymphocytes. The mucosa and villi were intact but somewhat flattened. Chemical analysis of the paste revealed: calcium carbonate, 81.3 per cent., calcium

phosphate, 0.5 per cent.; the rest organic matter. The mucus showed bile pigment present and cholesterol absent.

Case IV.—E. J., female, aged twenty-nine years. During the past four months the patient had had about ten attacks of pain in the epigastrium, sometimes radiating to the right scapular region, lasting from a few minutes to six hours. Vomiting in about one-half of the attacks. No fever or jaundice. Past history negative aside from childhood diseases.

Physical examination revealed a well-developed white woman. Regional examination essentially negative aside from slight tenderness in the right upper quadrant of abdomen. No mass in gall-bladder region. A röntgenogram (Fig. 12) revealed small,

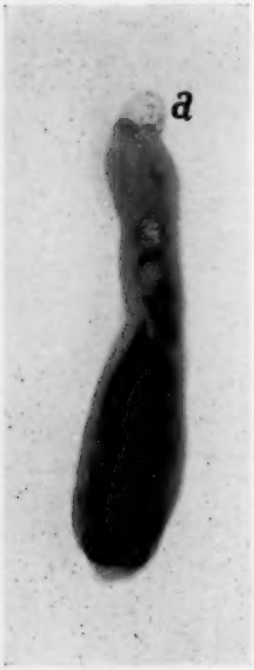

Fig. 13.

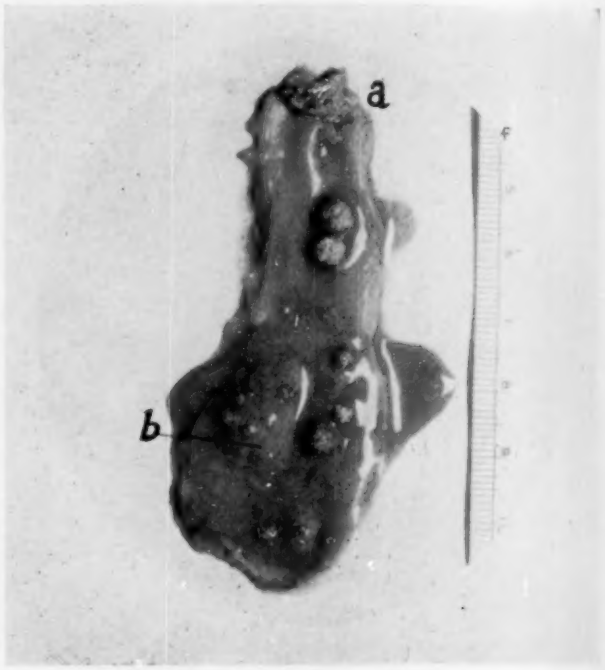

Fig. 14.

Fig. 13.—(Case IV.) Röntgenogram of specimen; (a) is crushed stone in cystic duct.
Fig. 14.—(Case IV.) Gall-bladder opened showing its content of stones, mucus and calcium carbonate; (a) is crushed stone in cystic duct, and (b) the largest mass of calcium carbonate incorporating cholesterol-pigment stones.

dense, oval, radio-opaque shadows along the course of the gall-bladder. The largest one at the lower end incorporated a circular radio-translucent area. Cholecystography showed no change in X-ray appearance after dye. A diagnosis was made of cholelithiasis, calculous obstruction of cystic duct and calcium carbonate deposit in gall-bladder about stones. At operation the gall-bladder was small, flaccid, slightly thickened and contained small stones. There was a stone in the cystic duct. Cholecystectomy.

A röntgenogram of the specimen (Fig. 13) showed a heavy, radio-opaque shadow about or incorporating radio-translucent stone shadows with speckled dense surfaces. The gall-bladder was partly collapsed and measured seven centimetres in length. Its wall was slightly thickened. On section it contained a few cubic centimetres of a dark green, stringy, thick mucus. There were eight brown gall-stones, varying from one-third to two-thirds centimetre in diameter, in the gall-bladder, and one crushed stone in the cystic duct. In addition there were three oval, putty-like, gray masses in the gall-bladder, the largest being two centimetres long and incorporating four small brown stones. (Fig. 14.) Cholesterol and bile pigment were present in the mucus. Cultures

of the bile revealed no growth on blood-agar plates, Rosenow's media and plain broth in eight days.

Microscopical examination of the gall-bladder wall revealed the mucosa intact and very slight fibrosis and scattered lymphocytic infiltration of the muscularis and serosa.

The paste was removed from the specimen but was lost so that no chemical analysis was obtained, but its likeness to the other cases is so great that its nature can scarcely be questioned.

Case V.—J. R., male, aged thirty-seven years, complained of attacks of fullness of the stomach, belching and epigastric distress for ten years and of occasional sharp attacks of epigastric pain lasting from a few minutes to hours during the past two years.

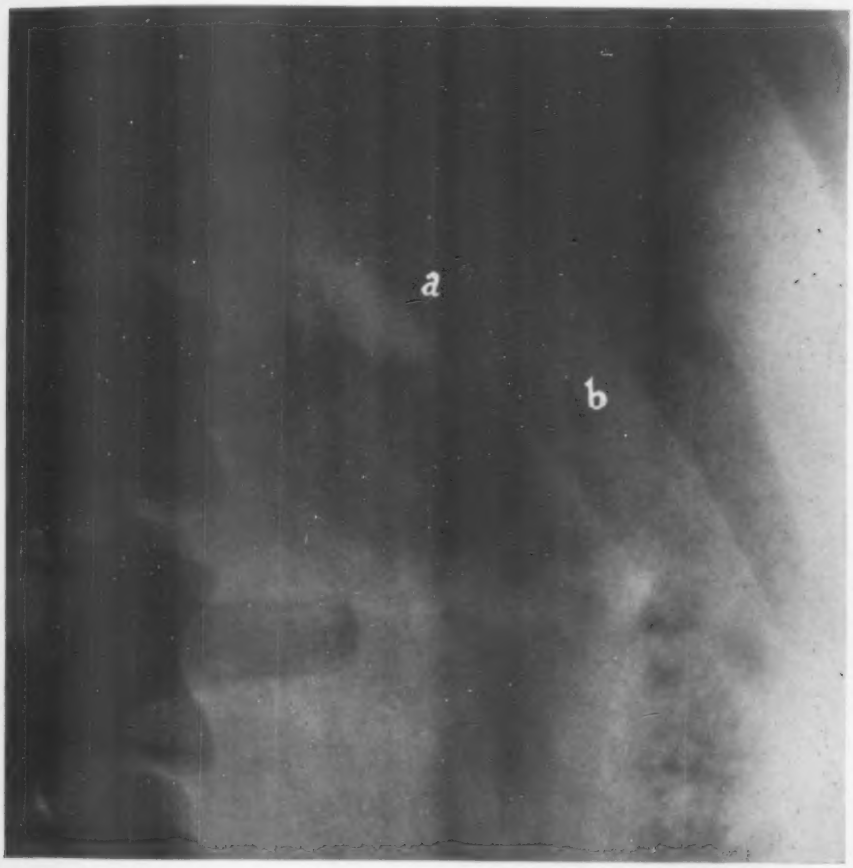

Fig. 15.—(Case V.) Röntgenogram showing radio-opaque shadow in region of cystic duct (a) and gall-bladder (b).

He has never been laid up with the attacks and there has been no accompanying jaundice or fever. Physical examination was essentially negative. There was no mass, tenderness or rigidity in the gall-bladder region. A röntgenogram (Fig. 15) revealed a dense oval shadow one and one-half centimetres long, lying below the right twelfth rib and a faint shadow in the region of the cystic duct. Cholecystography showed non-visualization of the gall-bladder. The diagnosis was made of calculous obstruction of cystic duct and calcium carbonate deposit in the gall-bladder.

At operation the gall-bladder was found collapsed and shrunken to about five centimetres in length. A stone was felt in the cystic duct. Cholecystectomy including the portion of the cystic duct containing the stone. A röntgenogram of the specimen (Fig. 16) revealed an oblong, fragmented shadow two centimetres long in the fundus of the

gall-bladder and a spherical shadow in the cystic duct. On section the gall-bladder contained a small amount of dark, thick, mucus and in the fundus an oval mass of gray paste which had been broken up by handling. There was a cholesterol stone in the first portion of the cystic duct with a brown deposit on its surface. (Fig. 17.) Microscopical sections of the wall revealed little fibrosis but areas of round-cell and eosinophilic infiltration of the wall. The epithelial lining and villi were intact. Chemical analysis of the paste in the gall-bladder showed it to contain a very high percentage of calcium and only a trace of phosphorus, but the amount was too small for a determination of the proportions of carbonate and phosphate.

Case VI.—T. T., female, aged thirty-seven years, was admitted to the University of Chicago Clinics September 12, 1930. For three years she had had occasional attacks of pain in the right upper quadrant lasting for a few hours, sometimes accompanied by vomiting. During the past year several attacks of painful and frequent urination which have at times coincided with the abdominal colics.

Fig. 16.

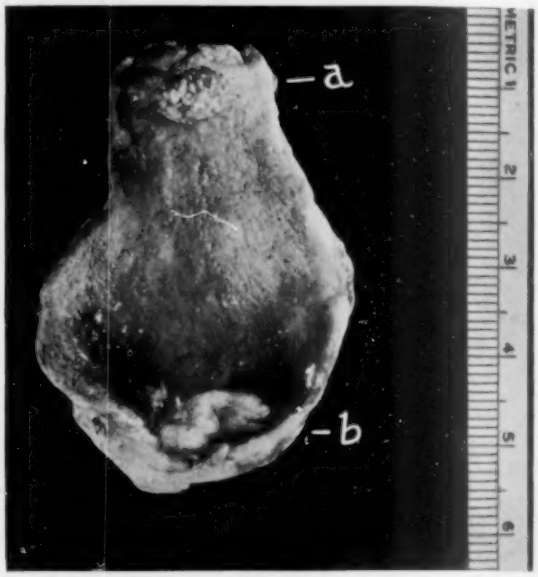

Fig. 17.

Fig. 16.—(Case V.) Röntgenogram of specimen showing (a) shadow of stone in cystic duct and (b) shadow of mass in gall-bladder.

Fig. 17.—(Case V.) Gall-bladder opened showing (a) cystic-duct stone and (b) calcium-carbonate paste in fundus.

Physical examination revealed a healthy-appearing, obese woman. Regional examination essentially negative aside from tenderness in the gall-bladder region. A röntgenogram (Fig. 18) revealed a circular, hazy, radio-opaque shadow in the gall-bladder region. No change in röntgenographic appearance after intravenous administration of tetiothalein. Urinalysis, cystoscopy and pyelography showed normal urinary tract. *Diagnosis.*—Calcium carbonate gall-stones. Patient refused operation but returned September 30, 1931, with history of a continuation of the same symptomatology and a severe right upper quadrant colic one week before, which had just worn off. Examination essentially negative aside from tenderness in the right upper quadrant. Urine negative. Operation October 2, 1931. The gall-bladder was slightly smaller than normal and distended with fluid. There was a stone in the cystic duct. No adhesions. Cholecystectomy including cystic duct containing stone.

An X-ray of the specimen (Fig. 19) showed an irregular granular dense shadow within the gall-bladder and a crescent-shaped dense shadow on the gall-bladder side of the stone in the cystic duct. Aspiration yielded twenty-five cubic centimetres of fluid which was placed under oil.

On section the gall-bladder wall was moderately thickened. There was a white deposit of dense, sand-like particles within the lumen as shown in Fig. 20. The stone in the cystic duct was about one centimetre in diameter and firmly anchored. It was pure cholesterol, with a thin white deposit on its gall-bladder side. Cultures of the fluid and gall-bladder wall on blood-agar plates and Rosenow's media remained sterile.

Chemical analysis of the sand-like deposit in the gall-bladder showed: Calcium carbonate, 99.4 per cent.; calcium phosphate, a trace; cholesterol and bile pigment, absent. Chemical analysis of the fluid aspirated from gall-bladder and centrifuged yielded calcium, 10.6 milligrams per 100 cubic centimetres; phosphorus, no reaction; CO_2, 11.25 volumes per cent.; pH, 6.82.

FIG. 18.—(Case VI.) Röntgenogram of gall-bladder before tetiothalein administration.

Animal Experiments.—Attempts were made to produce calcium-carbonate deposits in the gall-bladder by experiments on dogs, rabbits, and sheep.

EXPERIMENTS ON DOGS

Group I.—Ligation of the cystic duct. In none of the sets of experiments was the cystic artery identified and it was undoubtedly ligated along with the duct in many cases. The duct was ligated with silk in three animals, leaving the gall-bladder filled with bile. They were sacrificed in sixty-four, eighty-one, and 222 days. In the sixty-four- and eighty-one-day experiments the gall-bladders were slightly contracted and filled with a brownish-green mucus, the bile pigment not having been entirely absorbed. In the 220-day experiment the gall-bladder was about normal in size and filled with a semi-solid, grayish mucus. There was no evidence of stone nor of paste formation

within the gall-bladders and röntgenogram revealed no shadows suggesting calcium except a few extremely faint areas in the 220-day experiment. The mucus from it showed only 304 milligrams of calcium per 100 grams moist weight.

Group II.—Ligation of the cystic duct with subserous injection of one to two cubic centimetres of a suspension of twenty-four-hour blood-agar plate growth of *Streptococcus viridans.*

In seven experiments the ligated duct opened and bile reëntered the gall-bladder so that they were discarded. In eight experiments the duct remained closed and the animals were sacrificed after fifty-five, sixty-nine, eighty-five, ninety-eight, 105, 120, 121, and 220 days.

In the fifty-five-day experiment the gall-bladder was shrunken into a small, fibrosed mass.

In the sixty-nine-day experiment the gall-bladder contained twenty-five cubic centi-

FIG. 19.

FIG. 20.

FIG. 19.—(Case VI.) Granular dense shadow in gall-bladder and dense deposit on gall-bladder side of stone in cystic duct (a).

FIG. 20.—(Case VI.) Gall-bladder opened showing white sandy deposit of calcium carbonate and exposed cholesterol stone in cystic duct (a).

metres of a dark brown fluid. There were about a dozen pinhead-sized soft masses that gave a positive test for bile pigment. The fluid contained calcium, 46.3 milligrams per 100 cubic centimetres; CO_2, sixty-four volumes per cent.; and pH, 6.87. The gall-bladder wall showed almost no change.

The eighty-five-day experiment disclosed a bile-stained, richly mucous fluid in the gall-bladder with little change in the wall. X-rays of the specimen were negative for calcium shadow.

The ninety-eight-day experiment revealed a gall-bladder about one-half the normal size, with a much indurated wall. X-ray of the specimen showed no calcium shadow. On section it was filled with a very thick mucus which was stained dark brown from the old bile.

The 105-day experiment revealed a moderately thickened, slightly contracted gall-bladder which, on X-ray examination, cast no calcium shadow. It contained ten cubic centimetres of a viscid brown fluid, chemical examination of which revealed calcium, 43.6 milligrams per 100 cubic centimetres; phosphorus, a trace; CO_2, 671 volumes per

cent.; and pH, 6.67. Gram-positive rods were found in smears of the fluid and anaërobic milk cultures showed stormy fermentation.

The 120-day experiment revealed a shrunken gall-bladder filled with a thick gelatinous fluid which on X-ray examination cast no calcium shadow.

The 121-day experiment revealed a markedly thickened gall-bladder buried between liver lobes and a large inflammatory tumor mass in the adjacent liver. A röntgenogram revealed no calcium shadow. Ten cubic centimetres of turbid white fluid were aspirated. Cultures yielded a growth of *Staphylococcus albus*. There was no solid material in the gall-bladder. Chemical examination of the fluid showed calcium, 11.7 milligrams per 100 cubic centimetres; CO_2, 115 volumes per cent.; and pH, 7.45.

The 220-day experiment showed a moderately shrunken gall-bladder filled with a thick, gelatinous mucus and röntgenograms showed no calcium shadow. Cultures on blood-agar plates remained sterile.

It was apparent that the injection of the streptococci had had little permanent effect. In only one experiment (121 days) did the gall-bladder have the appearance of being extensively infected, but the organism cultured from it was a staphylococcus. In no case did the X-ray cast a shadow suggesting calcium-carbonate deposit and chemical analysis of the fluids in three cases showed the concentration of calcium and carbonate ions much below the level required for calcium-carbonate precipitation.

Group III.—Streptococcus injection of the wall of the gall-bladder. Fourteen experiments were performed in which one to two cubic centimetres of a suspension of a blood-agar-plate twenty-four-hour culture of *Streptococcus viridans* were injected beneath the serosa of the gall-bladder and the animals sacrificed at thirty-three to 134 days. On examination, the gall-bladders appeared to be practically normal. No mucus nor stone was found in the lumen which contained a normal-appearing bile.

Group IV.—Cystic-duct ligation with removal of bile and insertion of a human cholesterol-pigment stone, two-thirds centimetre in diameter, into the gall-bladder, and injection of one and one-half cubic centimetres of *Streptococcus viridans* beneath the serosa. One experiment. The dog was killed after 298 days. The gall-bladder was adherent to the surrounding liver, in which there was a hard, inflammatory mass one to two centimetres thick, extending the entire extent of its bed. It was distended with fluid and its wall thickened and indurated. The cystic duct was dilated for two centimetres down to the point of occlusion. An X-ray of the specimen including the liver showed a dense, granular, circular deposit two centimetres in diameter in the region of the gall-bladder. Eighteen cubic centimetres of a turbid, whitish fluid were aspirated. On section a yellowish-white, hard, sand-like deposit was found in the gall-bladder and the human stone was unchanged. Fig. 21 shows a photograph of the gall-bladder and duct dissected free with the human stone removed, but containing the sandy deposit. A röntgenogram (Fig. 22) shows the sand to cast a heavy, granular shadow. Cultures of the fluid yielded *Streptococcus viridans*. Microscopical examination showed considerable fibrosis and a small amount of leucocytic infiltration of the wall of the gall-bladder. Mucosa was intact. Chemical analysis of the sandy deposit showed calcium carbonate, 70.7 per cent.; calcium phosphate, 1.8 per cent.; the rest was organic matter. Chemical analysis of the supernatent aspirated fluid showed calcium, 12.1 milligrams per 100 cubic centimetres; phosphorus, a trace; CO_2, 112.8 volumes per cent.; and pH, 7.28. This represented a concentration of calcium and carbonate ions which exceeded tenfold the solubility product constant necessary for the precipitation of calcium carbonate. It contained 150 milligrams of cholesterol per 100 cubic centimetres. A test for bile pigment was negative.

This experiment duplicates the picture of calcium-carbonate deposition in the lumen of the gall-bladder in the human cases. The deposit is in the same form as that of Case VI.

RABBIT EXPERIMENTS

In two rabbits the cystic duct was ligated and one cubic centimetre of a streptococcus injected beneath the serosa. The animals were killed in twenty-two and 113 days. In the twenty-two-day experiment the gall-bladder was slightly contracted and contained mucous material but cast no calcium shadow in the X-ray. In the 113-day experiment the gall-bladder was small and filled with a thick pus which cast a few small shadows of calcium density in the X-ray.

In five rabbits the cystic duct was ligated and a small cholesterol-pigment human stone inserted in the empty gall-bladder. The animals were sacrificed in 135 to 245 days. The gall-bladders were small and three of them showed faint, irregular shadows of calcium deposits in röntgenograms of the excised specimens. On section the implanted stones were found unaltered in all cases and the cavities contained two to four cubic centimetres of a thick inspissated exudate. Chemical analysis showed the presence of calcium.

In two animals the cystic duct was ligated, the gall-bladder emptied, a small human

FIG. 21.

FIG. 22.

FIG. 21.—(Dog. 22.) Opened gall-bladder showing calcium-carbonate sand in it 298 days after tying cystic duct.

FIG. 22.—(Dog. 22.) Röntgenogram of specimen in Fig. 21, showing granular shadow of calcium carbonate in the gall-bladder.

stone inserted and streptococci injected beneath the serosa. One animal was killed in 137 days. The gall-bladder was moderately thickened and distended with fluid. A röntgenogram of the specimen including the liver revealed a ring-shaped shadow on the surface of the inserted gall-stone, which was present in a röntgenogram taken before its implantation. There were heavy, small, blotchy shadows about the region of the fundus of the gall-bladder.

The three cubic centimetres of clear fluid aspirated from the gall-bladder were insufficient for chemical analysis. There was a slight sediment when the bladder was opened and the wall was moderately thickened. The shadows in the fundus region were of calcium density and a chemical test for calcium was positive but the sediment was too scanty for analysis for carbonate and phosphate content. The other animal was sacrificed in 243 days. The gall-bladder was contracted and filled with a creamy, mucopurulent material. A röntgenogram revealed no shadow cast by either the exudate or the stone in the gall-bladder. The calcium deposits are similar to those produced in the rabbit by Wilkie.

In four rabbits a human stone was inserted into the gall-bladder without duct

ligation or bacterial injection. One animal killed in sixty-two days showed the gall-bladder normal but the stone which weighed .0176 gram before insertion had been reduced to .0112 gram. A second animal killed in 137 days showed no changes in the gall-bladder but the gall-stone had been about one-half absorbed. The third animal killed in 235 days and the fourth in 245 days showed complete disappearance of the gall-stones and no changes in the gall-bladder wall. Similar absorption of human gall-stones from the gall-bladder of dogs has been reported by others, as Walsh and Ivy.[3]

SHEEP EXPERIMENTS

In one sheep the cystic duct was ligated and a stone inserted into the gall-bladder. After 133 days the gall-bladder was found to contain a thick mucus with little change in the wall and röntgenologically there were no calcium shadows to be seen. The inserted stone was unchanged. In a second sheep the cystic duct was ligated and a human cholesterol-pigment stone weighing 0.206 gm. was inserted and streptococci injected beneath the serosa. After 281 days the gall-bladder was found contracted on the stone and containing no fluid. Its wall was fibrosed and the stone was unchanged.

A review of the animal experiments shows that one solid deposit of calcium carbonate in the gall-bladder similar to human Case VI was produced in the dog by cystic-duct ligation and streptococcus injection, setting up a chronic cholecystitis. The implanted human stone was unchanged and appeared to play no rôle. Faint calcium deposits were present in the mucus within the gall-bladders of five rabbits after cystic-duct ligation with bacterial injection in one, bacterial injection and stone implantation in one, and stone implantation in three. The dog experiments contradict the claim of Naunyn that the calcium is secreted with the mucus in that in most of the ligations of the cystic duct of long standing the gall-bladder was filled with very thick mucus and still there was no deposit of calcium carbonate.

Discussion.—The morphological conditions under which calcium carbonate had precipitated from the fluid in the gall-bladder in the human cases observed and in the experimental animals are: (1) Obstruction of the cystic duct, and (2) low-grade chronic inflammation of the gall-bladder with occasional slight exacerbations as indicated by the attacks of colic. The chemical composition of the gall-bladder contents found under these altered morphological conditions gave evidence that calcium and carbonate ions had accumulated to such an extent that the solubility product constant of calcium carbonate had been exceeded and the precipitation of calcium carbonate had resulted. Inorganic phosphate was present only in such small amounts that the solubility product constant of calcium phosphate had been rarely exceeded, and consequently only traces of solid calcium phosphate were found.

It is not possible as yet to state with exactitude the calcium-ion concentration in the gall-bladder fluids analyzed. There was so little exudate and so much mucus in five of the human cases that an analysis was impossible. However, if in the cases where fluid is obtainable one assumes that all of the calcium present in solution is in ionic form; and if one calculates the carbonate concentration from the pH and CO_2 according to the equations of Hastings, Murray and Sendray, one may determine whether or not the product (Ca) by (CO_3) is of an order of magnitude compatible with the existence of solid calcium carbonate.

This was done for fluids from the gall-bladders of Case VI and Dog

No. 22 (Fig. 21) both of which contained solid calcium-carbonate deposits.

The equilibrium product, 4 by 10^{-8}, was exceeded tenfold in the dog fluid. In Case VI it was not equalled but an acute attack of cholecystitis had just preceded the cholecystectomy, which may have been responsible for fresh exudation that temporarily lowered the ionic concentration. In fluids from a case of hydrops of the gall-bladder secondary to obstruction of the ampulla by a large cholesterol stone which previous to engagement had acquired a ring deposit of calcium carbonate the product (Ca) by (CO_3) was only one-tenth that required for the existence of solid calcium carbonate. It is noteworthy that from röntgen ray and gross examination calcium carbonate appeared to have been dissolved off the end of the stone protruding into the cavity, since the fluid had accumulated.

It is not possible at the present time to offer an adequate explanation for the accumulation of calcium and carbonate, and the total or almost complete absence of inorganic phosphate within the gall-bladder under the conditions just described. As a working hypothesis one may assume the entrance into the gall-bladder of an exudate, practically free of inorganic phosphate with a normal concentration of calcium and bicarbonate. This exudate is unable to leave the gall-bladder, however, due to the obstruction of the cystic duct. Consequently, upon subsequent concentration of the fluid either as a result of subsidence of inflammation or by the special concentrating power of the gall-bladder such as it exercises on bile, conditions are rendered favorable for the precipitation of calcium carbonate. That another lining membrane will hold back inorganic phosphate was shown by C. B. Huggins,[4] who found it completely lacking in spermatocele fluids. Another hypothesis would be to assume that the mucosa of the gall-bladder under these altered morphological conditions "secretes" calcium carbonate as the gastric mucosa secretes hydrochloric acid.

CALCIUM CARBONATE DEPOSITS ON GALL-STONES

The demonstration that the calcium carbonate forming separate deposits in cases of cystic-duct obstruction comes from the wall of the gall-bladder has raised the question as to whether the calcium carbonate deposited secondarily on the surface of cholesterol or cholesterol pigment stones also comes from the wall of the gall-bladder and of the possible relationship of the occurrence to temporary gall-bladder stasis produced by either calculous obstruction complete or incomplete or by inflammation.

Cholecystography was carried out on forty-four of the forty-eight cases operated on after intravenous tetriodthalein administration. In twenty-five of these no shadow was present in the gall-bladder region in the preliminary röntgenogram. Six of these showed normal, and seven subnormal visualization after dye administration with radio-translucent stones. One showed faint visualization but no radio-translucent stone and operation revealed numerous small stones. Nineteen cases showed radio-opaque shadows in the gall-bladder region before dye administration. Deducting the six with cystic-duct obstruction and separate calcium carbonate deposits there were

thirteen cases in which the stones alone cast radio-opaque shadows. Cholecystography in these cases showed non-visualization of the gall-bladder by the dye in ten, poor visualization in one and good visualization in two. The calcium was in the form of a secondary or ring deposit in the stone in all cases except one, in which there was good visualization. In that case it was largely a nuclear deposit. In the thirteen cases a stone in the cystic duct was found at operation in only one.

The analysis shows that when ring deposits of calcium carbonate casting radio-opaque shadows were present on stones the concentrating function of the gall-bladder was lost in a very high percentage of cases, whereas it was present in normal or reduced amount in the majority of cases of gall-bladders containing radio-translucent stones. How much this tendency to ring deposits of calcium on stones in gall-bladders with loss or marked impairment of concentrating function was due to obstruction and how much to disease of the gall-bladder wall it was difficult to determine, but both factors undoubtedly played a rôle. A stone may obstruct temporarily after which it either passes back into the gall-bladder or on through the ducts. That the calcium may be laid down on the stones during periods of stasis is indicated by the fact that ring deposits were present on stones in four of the six cases of duct obstruction with separate calcium carbonate deposits. Fig. 23 is a röntgenogram of a gall-bladder, the cystic duct of which was partially obstructed by a stone at the orifice. It contained a dark, stringy bile. Calcium carbonate apparently was being laid down on the cholesterol-pigment stones that were present and also there was a small soft mass that was being deposited separately as seen in the röntgenogram.

Summary.—Among forty-eight consecutive cases operated on for gall-stones the cystic duct or ampulla was obstructed by stone in eleven, or 22.88 per cent. Five of these cases, or 10.4 per cent., presented the picture of ordinary hydrops of the gall-bladder. The remaining six cases, or 12.48 per cent., presented separate deposits in a partially collapsed gall-bladder of calcium carbonate varying in density from a mucous suspension in one case to a semi-solid paste in four cases and a dense coarse sand in one case.

A solid coarse sand-like deposit of practically pure calcium carbonate was produced experimentally in the dog by ligation of the cystic duct, injection of streptococci and implantation of a human stone in the gall-bladder. Small calcium deposits were obtained by similar procedures in rabbits. From the human cases and the animal experiments it appears that obstruction to the outlet of the gall-bladder at least of a high degree and a low-grade chronic inflammation are essential for the formation of separate deposits of calcium carbonate in the gall-bladder. The limited chemical analysis of gall-bladder fluids indicates that the calcium carbonate is precipitated from a solution in which calcium and carbonate ions accumulate in amounts which exceed the solubility product constant. The calcium is derived from the wall of the gall-bladder. The absence of cholesterol in the fluid beyond the amounts contained in exudates speaks against the wall of the gall-bladder being the source of cholesterol in gall-stones.

It was apparent from a study of the series of cases in which cholesterol or cholesterol-pigment gall-stones contained secondary ring deposits of calcium carbonate, with cystic duct either obstructed or unobstructed that the calcium carbonate is laid down in gall-bladders with disturbed or lost concentrating function either as a result of inflammation or of inflammation plus calculous obstruction complete or incomplete. The conditions indicate that the ring deposits of calcium carbonate come from the wall of the gall-bladder.

FIG. 23.

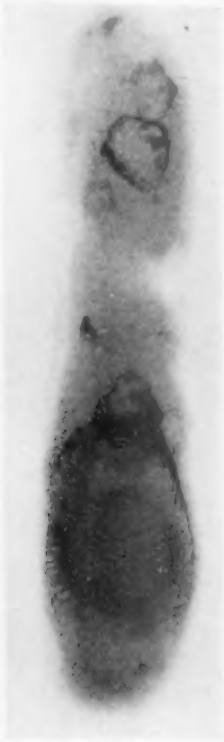

FIG. 24.

FIG. 23.—Röntgenogram of liver and gall-bladder of a rabbit 137 days after ligation of cystic duct, insertion of human stone, and injection of streptococci in wall; (y) is calcareous shadow within the fundus of gall-bladder; (x) is human stone at its outlet.

FIG. 24.—Röntgenogram of gall-bladder with loose obstruction of cystic duct by stone. Calcium-carbonate deposition taking place simultaneously on surface of cholesterol-pigment stones and as independent flakes in its fluid content.

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THE MECHANISM OF CHOLESTEROL GALL-STONE FORMATION

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In a series of recent communications,[1, 2, 3] it was shown that the cholesterol in the bile was held in solution in a chemical combination with the bile salts. Experiments, *in vitro,* indicated that this complex could be broken up by dialysis, the bile salts passing through the membrane and the cholesterol being left behind and precipitated. Analyses of the bile of normal and diseased gall-bladders both in dogs and human beings indicated that while the normal gall-bladder was impermeable to bile salts, the diseased viscus was quite permeable and acted as a dialysing membrane, permitting the solvent, the bile salts, to pass out and the cholesterol to be precipitated with the consequent implication of gall-stone formation.

Our experiments indicated that on the average thirteen molecules of bile salt were necessary to hold one of cholesterol in solution. Owing to variations in the type of bile salt as well as other unknown factors, this figure is only approximate and varies between ten and fifteen. In other words, if the bile salt-cholesterol ratio is below thirteen the bile is saturated and precipitation is liable to occur. In normal human bile, according to the analyses of Hammarsten,[4] the bile salt-cholesterol ratio is forty. The more recent studies of Newman[5] put the figure at seventeen. These analyses were made on post-mortem material and the figures probably err slightly on the lower side, as it is obvious from the work of Whipple[6] and our own experiments[7] that during the agonal period the secretion of bile salts would be at a minimum. This fact is borne out from a study of our own operative specimens. They include biles removed from gall-bladders, which were not diseased (cholecystenterostomy, four cases; common-duct exploration, two cases; normal gall-bladders on histological examination post-operative, three cases). In this series of nine cases the bile salt-cholesterol ratio was twenty-five. (Table I.)

In very striking contrast was the analysis of bile removed from diseased gall-bladders. Our series of analyses has now been extended to fifty-three. In this entire series the bile salt-cholesterol ratio was 2.5. This is exactly one-tenth of the ratio in the control series and to our minds offers quite definite proof that the diseased gall-bladder absorbs bile salts at the expense of cholesterol. Further proof is that in all gall-bladders in which cystic-duct obstruction has been present for long periods the bile salts had all been absorbed and the cholesterol was not held in solution, and the oft-observed fact that in biles not containing any bile acid the cholesterol was entirely in crystalline form and not in solution.

It has been stated from the time of Naunyn that cholesterol was excreted by the gall-bladder wall. If this were a fact it would of course offer an obvious explanation of the above findings. Our experiments, however, have

TABLE I.

ANALYSES OF BILE FROM NORMAL AND DISEASED HUMAN GALL BLADDERS

No. of cases		B.S./Chol. Ratio
2	Hammarsten (normal)	40
11	Newman (normal)	17
9	Our controls	25
51	Diseased gall bladders	2.5

failed to substantiate this claim. Table II, taken from a recent publication, shows beyond a doubt that the gall-bladders, of dogs at least, do not have this function. While common-duct ligature has been shown to produce some

TABLE II.

CHOLESTEROL CONTENT OF GALL BLADDER BILE IN STASIS

Controls 36 dogs with stasis of 24 hours or less	Average 57 Mg per 100 cc.
42 dogs with common duct ligature 3-58 days	Average 51 Mg per 100 cc.

slight changes in the histological appearance of the gall-bladder as well as the finding of bacteria in the ordinarily sterile dog bile, the changes are not marked and evidently do not interfere with the normal absorptive mecha-

TABLE III.

ANALYSES OF BILE FROM NORMAL AND DISEASED DOG'S GALL BLADDERS

No. of exps.		Bile Salts	Chol.	B.S./Chol. Ratio
81	normal controls	3630	55	66
57	diseased	1028	47	24

Figures for bile salts and cholesterol in milligram per 100 cubic centimetres. Cystic ducts closed.

nism. If the gall-bladder has a cholesterol-secreting function it is inconceivable that it would not become evident in such a long series of experiments as this. Further data on this subject are given in a previous paper.[8]

In our original publications,[2] experiments were cited showing that the gall-bladder of the dog, if diseased, absorbed bile salts at the expense of cholesterol. Since then these observations have been markedly extended. Table III is a summary of the analyses of 138 dogs' bladder bile and amply confirms our previous reports. The numbers involved are quite sufficient to rule out the possibility of the results being explained as due to the wide normal fluctuations in the chemical contents of dog bile. While the cholesterol content of bile from diseased gall-bladders lies quite within the normal range, the bile-salt content is reduced about 65 per cent.

The term "diseased gall-bladder" has been used in this paper with intentional vagueness, as it has been quite difficult to explain just what factors bring about abnormal absorptive phenomenon. These factors may be grouped under four heads: (1) Infection, (2) stasis, (3) circulatory changes, and (4) chemical damage, from the entrance of pancreatic juice as suggested by Wolfer, or even intestinal juices.

In these studies it has proven very difficult to differentiate the factors of stasis and infection. Does stasis or infection, or both, cause the absorption of the bile salts and hence gall-stone formation? The separation of these two factors is so difficult because each in turn will cause the other. In a previous communication[9] it was shown that ligature of the cystic duct in dogs caused the prompt invasion of the gall-bladder by the rich liver flora. This has been demonstrated both bacteriologically and histologically in over fifty dogs. Ligature of the common duct with resultant stasis produces also slight inflammatory changes, but to a very much smaller degree. Recent experiments have shown that in dogs at least the gall-bladder infected by injection of an emulsion of streptococci under the serosa fails to visualize after intravenous iodokon injection. Examination of such a gall-bladder reveals the fact that for a week or two after such infection the cystic duct appears to be swollen shut.

With the object of attempting to evaluate the importance of these four factors and to determine the importance of each in gall-stone formation the following experiments were undertaken.

Stasis.—While as above stated the production of stasis by common-duct ligature is not entirely free from criticism on the basis of resultant infection, this infection is in most cases minimal and the gall-bladder remains grossly normal although histological changes are usually found. The following series of experiments therefore may be said to show the effect of stasis alone, or at least with the least possible element of infection superimposed. The new element of jaundice is of course introduced, but this is unavoidable. The secretion of the damaged liver as has been shown by a number of observers, is much more apt to have a low bile-salt content than a low cholesterol content. The reports of Whipple,[10] Walters,[11] and Andrews[7] may be cited on this issue. In view, however, of the negative character of the results found, this fact only adds to the value of the conclusions.

Fifty-one dogs were used. Ten were controls, sacrificed after a short period of starvation. The remaining forty-one were operated upon under ether anæsthesia and the common duct ligated as close to the duodenum as possible. These dogs were kept on an ordinary mixed diet. Some died and some were sacrificed at various periods up to eighty days. The cystic ducts were clamped, the gall-bladders excised and emptied. In each case the amount of bile salts was determined by the amino-nitrogen method and the cholesterol colorimetrically.

The data thus acquired are given in Table IV.

The results of these experiments are so clear-cut as hardly to require any comment. While, as in all dog experiments, the individual figures varied rather widely, the average for the different groups fell quite within the limits of experimental error. The bile salt-cholesterol ratio for each of the groups was approximately the same and there is no tendency for the later

TABLE IV.

EFFECT OF STASIS ON BILE SALT - CHOLESTEROL RATIO

	No. of Exps.	Chol.	B.S.	B.S.-Chol. ratio
Controls	10	67	3650	54
1 day	5	56	3002	54
3-5 days	9	69	3157	45
6-12 days	12	77	4741	61
12-42 days	8	24	1219	52
44-80 days	7	41	2034	49

Figures for bile salts and cholesterol in milligram per 100 cubic centimetres. Stasis produced by ligature of common duct near duodenum.

figures to be smaller. In other words, in long-continued stasis produced by common-duct ligation there is quite definite evidence against any excretion of cholesterol by the gall-bladder wall, as well as evidence against any differential absorption of bile salts at the expense of the cholesterol. The bile salt-cholesterol ratio is not lowered by stasis in the gall-bladder alone and the introduction of some other factor is necessary. Differences in the absolute value of bile salts or cholesterol are explained by varying amounts of water in the gall-bladder. In view of the possibility of flow back and forth into the dilated common duct, no studies of the total gall-bladder contents were made.

Infection.—Since stasis alone is shown not to cause absorption of bile salts, the effect of bacterial injection was tried. The materials injected were first streptococci and secondly a filtered emulsion of dogs' fæces. The

latter were used in place of pure cultures as it was thought they gave a better general representation of the intestinal flora. The gross effects of the streptococci were much less than of the fecal emulsion. Nine experiments in which they were injected into the subserous coats of the gall-bladder resulted in no chemical changes in the bile at all and are not included in the table. Introduction of either streptococci or fecal emulsion into the gall-bladder by needle puncture or injection up the common duct with a ureteral catheter into the gall-bladder as can be seen from Table V produced the prompt onset of profound chemical changes in the constituents of the bile. The degree of cholecystitis was severe and the bladders were shrunken and contained but small quantities of very inspissated bile. Several specimens

TABLE V.

INJECTION OF BACTERIA INTO DOG'S GALL BLADDER

No. Exps.		B.S.	Chol.	B.S./ Chol.
4	2 cc cloudy suspension of streptococcus injected up common duct into gall bladder with catheter.	1706	92	19
2	2 cc same thru needle puncture into lumen.	1545	111	14
4	2 cc filtered emulsion dog feces up duct.	88	86	1
3	2 cc same into lumen	217	118	2
2	2 cc same subserous	1230	300	4
	Average	893	126	7
81	Normal controls	3630	55	66

Figures for bile salts and cholesterol in milligram per 100 cubic centimetres. Duration of experiments four days.

not included in the table had to be discarded as there was not sufficient bile for analysis. The results shown indicate that the factor of infection is the important one in bringing about bile-acid absorption. In the experiments with the streptococcus the lowering of the bile salt-cholesterol ratio is moderate, the average being twenty-two against a normal of about sixty-six for dogs. In the case of the fæces it corresponds with the obvious gross changes and is much more marked.

It has been stated by some observers that the action of bacteria alone on bile is capable of destroying the bile acids or cholesterol. Most of this work was done before the advent of modern chemical methods of bile-salt analysis. All workers with sterols have long recognized their extraordinary resistance to bacterial action. Even when incubated with fæces or passed through the

gastro-intestinal tract they may be recovered quantitatively. The cholic-acid radical which is extraordinarily similar to cholesterol is similarly resistant. It is true that the combined bile acids may be hydrolyzed by bacteria to form simple ones plus glycocoll or taurine, in which case they would not show on amino-nitrogen determinations. This, however, occurs only in the presence of marked putrefactive changes and in short-time experiments such as reported here is not a factor in the results, as is shown by the following experiments. Five per cent. solutions of bile salts were inoculated with a loopfull of streptococci, staphylococci, *B. coli* and *B. Welchii* and fæces. Analyses of samples of this mixture were made at once, in twenty-four hours, three days and five days. In no case was there found any appreciable lessening of the combined bile acids, although all the solutions had become cloudy with bacteria. A series of thirty-six such analyses was made and in no case was evidence forthcoming of any destruction of bile acids. One must conclude, therefore, that our previous experimental findings represent an absorption, not a destruction, of bile acids.

In these experiments it is seen that there is an increase in the cholesterol content of over 100 per cent. Such changes have been interpreted by Naunyn,[12] and, more recently, by Elman and Graham,[13] as indicative of excretion of cholesterol by the gall-bladder mucosa. While this factor may play a rôle it seems to us exceedingly unlikely that it is a major one for the following reasons: In experiments with gall-bladders in which cystic ducts are ligated there is no increase in the cholesterol content. Table III presents evidence on this score. Tables II and IV also indicate that obstruction of the common duct does not lead to accumulation of cholesterol in the gall-bladder. In this group (Table V) the cystic duct was open and it was quite possible for bile to continue to pour into the gall-bladder and the cholesterol to remain while the water and bile salts were absorbed. The results may also be explained by the fact that the gall-bladders' contents were considerably smaller at the end of the experiments than at the beginning and the rise in the cholesterol concentration may be simply due to concentration of the bile by absorption of water.

Circulatory changes.—These are almost impossible to evaluate. In the previously reported series of experiments where dogs' cystic ducts were tied, great care was taken to avoid the cystic artery and this was usually checked post-mortem. However, the blood supply to the dogs' gall-bladder is complicated and it is manifestly impossible to tie the duct without damaging the vascular elements. Microscopical examination of this region shows a very rich network of vessels closely associated with the duct, which must certainly be tied even if the main cystic artery is preserved. Therefore in such experiments circulatory changes cannot be ruled out.

A few attempts were made to ligate the artery without injuring the ducts. The results were so inconsistent that no detailed studies on this type of experiment can be reported.

Chemical irritation.—The possibility of reflux of pancreatic juice into the gall-bladder with resultant cholecystitis has been thoroughly reviewed

TABLE VI.

EFFECT OF PANCREATIC JUICE ON GALL BLADDER CONTENTS

No.	Experiment	Time Days	B.S.	Chol.	B.S./ Chol.
1	8 cc. Berkfeld filtered juice thru needle puncture.	4	2673	40	66
2	5 cc.	4	446	47	9
3	7	4	0	52	0
4	4	4	2232	43	51
5	5	4	2722	90	30
6	5	4	942	100	9
7	7	4	2417	47	51
8	5	4	1546	70	22
9	4	4	2947.	83	35
10	6	4	666	70	9
11	5	4	2920	62	47
12	2 cc. filtered juice thru common duct in g.b. Duct tied.	2	0	25	0
13	"	4	0	125	0
14	"	2	0	25	0
15	4 cc. unfiltered juice thru needle puncture.	4	0		0
16	"	4	0		0
17	"	4	0		0
18	"	4	0		0
19	"	4	0		0
	Average		1027	63	16
	Average 81 normal controls		3630	55	66

Figures for bile salts and cholesterol in milligram per 100 cubic centimetres.

recently by Wolfer[14] and needs no further discussion. The accompanying Table VI shows very clearly that in dogs at least this causes prompt changes

in the permeability of the viscus to bile salts, which are rapidly absorbed. There is a profound fall in the bile salt-cholesterol ratio to very low levels. While the cholesterol content of the bile remains about the same about one-third of the bile salts are absorbed and in many of the experiments, especially with the unfiltered juice, all the bile salts were absorbed. *In vitro* experiments show that these changes represent an absorption and not a destruction of bile salts by pancreatic juice. At any rate it is obvious from these results that pancreatic juice may be a factor in gall-stone formation.

This thesis is also supported by the following clinical observations. The bile and gall-bladder wall have been cultured in a series of twenty-three cases, which for various reasons must be classified as acute, either due to clinical activity present or less than three days pre-operative, and confirmed by the findings of leucocytic infiltration of severe degree. Fifteen of these cases showed either a sterile bile or sterile gall-bladder wall. Two of the cases were especially striking as they showed the gall-bladder grossly acutely inflamed and covered with fibrin, being very thick and white in color. The post-operative course of these two patients was also remarkable in being smooth, afebrile and not stormy, as was expected from the operative findings.

Thus, while entrance of pancreatic juice into the gall-bladder cannot be positively stated to be a factor in disease, it appears at least to be a possible one and amply deserves further study.

CONCLUSIONS

(1) Cholesterol gall-stones may result from the absorption of bile salts by the diseased gall-bladder with consequent precipitation of cholesterol.

(2) Cholesterol is not excreted by the gall-bladder mucosa.

(3) Stasis alone does not result in stone formation.

(4) Injury to the gall-bladder wall by bacterial or other toxic agents appears to be the important factor.

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DISCUSSION.—DR. EDWIN BEER (New York City) said if he understands the report of Doctor Phemister correctly, the production of the calcium deposits usually takes place in the obstructed gall-bladders, whether cystic obstruction be due to gall-stone or not, provided a mild inflammatory reaction persists in the mucous membrane and gall-bladder wall.

It is interesting to note that visualization of the gall-bladder stones is accomplished by virtue of the fact that a ring deposit of calcium is placed upon their nuclei by similar changes.

In the urinary bladder and the upper urinary tract there are non-opaque stones which are shown by röntgen-ray only after the mucous membrane of the bladder or the ureter has thrown down some calcium which deposits as a ring around the stones, making stones that previously were invisible stones, opaque to the röntgen-ray, a process analogous to that which is seen in the biliary tract.

As far as Doctor Andrews' presentation was concerned, it was very difficult to follow the tables, but the speaker had the impression from his own studies of the urinary and biliary tracts that the fundamental causative factor in the production of stones is collodial instability associated with stagnation; whether that is due to a diminution of the bile salts or whether it is due to some mucous-membrane change (avitaminosis?), he did not know. He also said if Doctor Andrews' conception as to the influence of the bile salts was correct, one would expect a regular deposition of crystalloids in one of the experimental series.

One of the most striking instances of this instability that he had observed had been in peripheral phosphaturia cases in the urinary tract. Here a patient may pass milky phosphaturic urine, and immediate catheterization of the bladder may show absolutely clear urine. Just what produces this upset in the urinary tract, or what induces the instability, whether changes in the hydrogen ion concentration, electrical reactions or what-not, is unknown. Such peripheral phosphaturias have developed in the short female urethra.

Whether the same thing happens in the biliary tract does not lend itself to study, but in the behavior of the kidney, ureter and bladder we can suspect a similar colloidal instability in the biliary tract underlying the deposition of crystals and stones.

DOCTOR PHEMISTER in reply to Doctor Beer remarked that both infection and obstruction are factors in the deposition of calcium carbonate in the gall-bladder. It does not appear that infection alone will make pure calcium carbonate gall-stones but ring deposits on pre-existing stones are laid down in its presence. Pure calcium carbonate as a separate deposit comes only with duct obstruction. In the reported cases of duct obstruction and calcium-carbonate deposition in the gall-bladder there was no evidence of cholesterol deposition from the gall-bladder wall and the fluid in the cases of experimental obstruction always contained less than 150 milligrams of cholesterol per 100 cubic centimetres, which is no greater than is ordinarily found in exudates.

DR. EDMUND ANDREWS (Chicago) said as to the question of sudden crystallization of supersaturated materials, it is obvious that the least temperature change, or trauma,

or anything else of that sort would explain the phenomenon that Doctor Beer spoke of as a "sudden colloidal change." When urine leaves the bladder and lands in a cold vessel, it will immediately crystallize, but those we mean are those that occur in the gall-bladder and not after it gets out.

As to the experiments of Doctor Wilkie his and one other set of experiments report the formation of cholesterol gall-stones in experimental animals. They are the only records that I know of that make such a report. I have repeated both sets and I have seen both sets repeated by other observers in a very large number of cases, and I have never heard of a cholesterol gall-stone formed in any experimental animal nor any animal except man. That is due to the fact there is not enough cholesterol in the bile of a dog. It is exceedingly low in a dog. In the liver bile it is ten milligrams and in the fistula bile it is less.

We have repeated the experiments reported and we were never able to find any cholesterol content. We never found any increase in the total cholesterol content of the gall-bladder. You get an increase in concentration due only to the absorption of water.

As to the relation of the blood cholesterol and gall-stones, the recent work of McNee and Campbell, and especially a long series of English observers, has completely dissociated any such factor whatsoever. Campbell does not know of any figures today that will demonstrate that there is any more cholesterol in the blood of a person with gall-stones than there is with a normal human being, and he knows a great many long series of figures that strongly controvert that point. He said we now know the vast majority of the cholesterol, according to the work of Sperry, is secreted in the bowel and not into the bile. The best example he knows of is that in the very high blood cholesterols, about the highest we find, in war œdemas and starvation œdemas, which is the one thing that will increase the cholesterol in the bile, he knows of no figures showing increase in the gall-stones in those cases. As to the secretion of the gall-bladder itself, they had done some experiments in which they have opened the gall-bladder of dogs, tied off the cystic duct, and made gall-bladder fistulæ. Such animals become promptly infected and have lots of pus containing a high percentage of cholesterol and a low percentage of calcium being strongly acid. However, in those in a long series, only one such experiment succeeded in that the gall-bladder subsequently closed and stayed clean. In that animal they got a cyst which was full of the same type of milky fluid Doctor Phemister found in the human being with obstruction, and it was all in crystalline form. It contained only twenty-one milligrams of cholesterol, so he thinks it shows that the probabilities are that the calcium is an excretion of the gall-bladder mucosa itself. Whether it is necessary that it should be mildly infected, it is impossible to say, because almost any dog preparation that we make is mildly infected.

TUBERCULOSIS OF THE THYROID GLAND

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A survey of the literature of the last decade suggests an increase in the incidence of tuberculous involvement of the thyroid gland, but this probably is relative rather than actual, due, no doubt, to the greater number of goitres that have been operated on during this period, and also to a progressive trend toward microscopical examination of the tissue removed at operation. The disproportion between the actual number of times the thyroid gland is involved in a tuberculous process and the number of times partial thyroidectomy is performed for any cause still remains so considerable as to permit a continuation of the appellation "rare" as hitherto applied to this disease. In the course of microscopical study of 20,758 thyroid glands removed surgically at The Mayo Clinic over a period of eleven years, tuberculosis was diagnosed twenty-one times, an incidence of 0.1 per cent.

Of general interest but of little clinical significance is a consideration of those cases in which the thyroid gland is found at necropsy to be involved in generalized, fatal miliary tuberculosis, with similar involvement of most of the other organs of the body. We are principally concerned here, however, with that form of involvement of the thyroid gland which gives rise to a clinical syndrome referable to thyroid dysfunction, but which, unfortunately, fails to produce symptoms that are peculiar or pathognomonic of tuberculous invasion of this organ.

Albers,[1] in 1847, is accredited by Foerster as being the first to have observed tuberculosis in the thyroid gland. Lebert,[47] in 1857, reported his observations made at necropsy of involvement of the thyroid gland in a fatal case of miliary tuberculosis. Four years later Rokitanski[68] made the unqualified statement that tuberculosis never involves the thyroid gland, and Virchow[80] was of the opinion that by some antagonistic action the association of goitre and tuberculosis is prevented except in extremely rare instances, the result of direct invasion from contiguous tuberculous structures. However, in 1865, he did report two cases of miliary tuberculosis and one of the caseous form observed at necropsy. Opinions of such a positive nature held by these two great pathologists of the middle of the eighteenth century were bound to influence thought along these lines. This probably explains the practice during the middle of the last century of sending patients with tuberculosis to regions in which goitre was endemic in the anticipation that the acquisition of goitre would influence the tuberculosis favorably. Hamburger[34] made the statement that a patient with goitre at least never acquires tuberculosis. It is not surprising, under these circumstances, that the condition should be entirely ignored or at least so briefly considered in the text-books of the time, such as those of Heschl,[37] Rokitanski,[68] Cruveilhier,[25] Wagner,[82] and Virchow.[80]

From the first reported case up to 1893, approximately 120 necropsies were recorded, 107 of which were incident to generalized miliary tuberculosis, whereas the remainder

were associated with chronic pulmonary or glandular tubercular processes. Of the total number, caseation was revealed in three. Cohnheim,[17] Cornil and Ranvier,[20] Demme,[24] Weigert,[88] Wölfler,[84] Berry,[9] Voelcker,[81] and Perry[67] reported one or more cases each, and Chiari,[15] Fraenkel,[29] and Hegar[36] furnished statistics which tended to show the incidence of involvement of the thyroid gland in fatal cases of generalized or chronic pulmonary tuberculosis. Cohnheim,[17] in studying choroidal tuberculosis in cases of miliary tuberculosis, rarely failed to note tubercles in the thyroid gland. The report of Cornil and Ranvier,[20] in 1870, which was the first account of a minute histological investigation, served as an impetus to more careful consideration of the histogenesis of tuberculosis of the thyroid gland. Quinlan,[68] in 1871, first suggested that the specific changes in the thyroid gland which could regularly be found in acute miliary tuberculosis could also be found in the chronic forms of pulmonary tuberculosis. This, together with his personal observation of the simultaneous occurrence of advanced pulmonary involvement and tubercles in a follicular struma, led Demme,[24] in 1878, to question the accepted antithesis between the thyroid gland and tuberculosis. Chiari[15] found invasion of the thyroid gland in seven of 100 carefully studied cases of acute and chronic tuberculosis; Fraenkel[29] found such invasion five times in a series of fifty necropsies in which chronic tuberculosis was demonstrated; Hegar,[36] in 1891, on the other hand, reported only fifty-seven instances of involvement of the thyroid gland at necropsy of 1,563 tuberculous subjects. Fraenkel's publication, in 1886, revealed a particularly thorough investigation of this subject. Nather[58] stated that after Koch's discovery of the bacillus of tuberculosis he was the first to look for the organism in its specific tissue, and after such studies he stated that the tubercles in the thyroid gland contained few bacilli, a fact he explained on the basis that either the bacillary invasion from the beginning was sparse, or that a large number of bacilli was rapidly destroyed; this latter conception appealed to him as the more likely. He also found the thyroid gland to be regularly involved in acute miliary tuberculosis but that relatively few cases were involved in chronic tuberculosis. Surgery in such cases, he stated, would be of no avail.

At the turn of the century, and particularly during the first decade of the present century, the knowledge of tuberculosis of the thyroid gland became more general. It is true that a few of the text-books such as those of Rindfleisch,[66] Langerhans,[46] and Schmaus[73] did not mention tuberculosis of the thyroid gland, but Ewald,[28] Eiselsberg,[27] Ziegler,[85] Ribbert,[65] Kaufmann,[43] and Aschoff[4] at least mentioned such an occurrence, and Bérard[8] considered the subject extensively. Although, during the previous fifty to sixty years, one was led to believe in direct antithesis between the thyroid gland and tuberculosis, at the beginning of the present century the relationship between the two was placed in a new light through the works of the French school. Morin,[54] in 1895, described sclerosis of the thyroid gland which he frequently observed following death from pulmonary tuberculosis; he reported 348 such cases. Morin observed that patients even with slight enlargement of the thyroid gland showed a greater tendency to improvement and eventual healing. This was in agreement with the frequent coexistence of myxœdema and tuberculosis, which Mackenzie[51] had previously pointed out. Lorand[50] observed also that tuberculosis occurred with marked frequency when the thyroid gland had been altered by disease or reached a state of exhaustion, or after pregnancy. Roger and Garnier,[67] in a comprehensive consideration of the sclerotic type of gland described by Morin,[54] reported having encountered it at necropsy of eleven of twelve tuberculous subjects. Their investigations were confirmed through the almost simultaneous studies of Charrin and Nattan-Larrier.[14] Besides sclerosis they observed proliferation of epithelium in the follicles, and concluded that they were dealing with a state of functional hyperactivity. Moreover, they demonstrated increased colloid content in the acute forms of tuberculosis as well as in other infectious diseases, whereas in cases that ran a chronic course, the colloid appeared to be decreased. They ascribed these changes to circulating tuberculous toxins in the blood and not to the bacillus of tuberculosis. A

distinction between this type of sclerosis and fibrosis secondary to bacillary invasion of the thyroid gland will be considered later. Torri,[77] Kashiwamura,[42] de Quervain,[62] and Costa[21] likewise have written on this subject. Kashiwamura,[42] in 1901, studied the thyroid gland at necropsy in a large number of cases of patients who had died of infectious diseases. Although he noted sclerosis almost invariably in cases of chronic tuberculosis, he was not inclined to ascribe such change to any specific influence of the bacillus of tuberculosis or its toxins, since he also demonstrated identical sclerosis of the interstitial tissue in typhus, diphtheria, and in a case of gas poisoning. The publications of Poncet and Keriche,[60] in 1906, and their school of thought popularized the conception of a close relation between tuberculosis and goitre. Nather[56] found that many cases of ordinary goitre as well as of other benign tumors were in a certain measure supposed to represent a kind of reaction product of a tuberculous infection in the body without, however, the formation of specific granulation tissue.

Costa[21] and Dumas[25] associated exophthalmic goitre with a sort of inflammatory tuberculosis in the thyroid gland, in which the specific lesion was absent. Hufnagel[40] supported this view, but with certain reservations, and the observations of Dunger,[28] and Apelt[2] that cases of exophthalmic goitre had developed at the termination of an acute infectious disease added further weight to such a contention. Moreover, the similarity in the histological changes in the thyroid glands of animals in which de Quervain[62] had demonstrated experimental thyroiditis, with the changes in exophthalmic goitre, appeared to indicate a certain relationship between infection and exophthalmic goitre.

Forty-six years after tuberculous invasion of the thyroid gland was first recognized pathologically, Bruns,[11] in 1893, reported what appears to be the first recorded instance in which the diagnosis was established at operation. The patient was a woman, aged forty-one years, who sought relief from pain from a goitre of long standing. Recurrent paralysis of the nerves was noted before operation. The gland removed at operation was studied by Baumgarten,[7] who saw proliferating follicular epithelium take part in the formation of tubercles by transformation into giant cells. Since this report approximately 104 additional clinical cases have been recorded. (Table I.)

Barth's[6] case, reported in 1884, as well as cases of several other observers, has not been included in Table I; although the patients showed clinical signs of dysfunction of the thyroid gland prior to death, they were not operated on. Moreover, there is some question in Barth's case of the changes in the thyroid gland being syphilitic.

In more than 95 per cent. of the cases it was possible to tabulate the age, sex, presence or absence of tuberculosis elsewhere in the body, type of operation employed and the pathological description of the thyroid tissue removed. There were eighty-three women and seventeen men; in four instances the sex was not given. The average age of the women was thirty-six and a half years, and of the men, twenty-six and eight-tenths years. The age incidence according to decades, in the cases reported in the literature and in the cases studied by us, is tabulated in Table II.

In ninety-seven of the 104 cases in which the information was obtainable there were six cases of tuberculosis elsewhere in the body, either at the time of examination or shortly before. Pulmonary involvement was noted in three cases, and tuberculosis of the knee and of the bone, and scrofula, each was recorded once. There were two cases of suspected pulmonary tuberculosis and a history of repeated attacks of pleurisy in three cases. Partial thyroidectomy was performed in ninety-four cases, incisions and drainage were done in eight and tracheotomy in one case. One patient was cured by the

TABLE I

Summary of Cases Reported in the Literature of Clinical Tuberculosis of the Thyroid Gland in Which Operation Was Performed

Author, Year	Cases	Age, Years and Sex	Evidence of Tuberculosis Elsewhere	Description of Process in Thyroid Gland	Treatment	Comment
Bruns[11] (1893)	1	41 F.	Glands of neck	Tubercles with giant cells in colloid gland	Thyroidectomy	Recurrent paralysis of nerves prior to operation
Schwarz[72] (1894)	1	30 M.	None	Cold abscess with tuberculous granulations	Incision and drainage	Recurrent paralysis of nerves prior to operation; organism recovered
Clairmont[16] (1902)	1	2	None	Tuberculous granulations	Incision and drainage	Compression of trachea required emergency operation
Pupovac[61] (1903)	1	42 F.	Lungs	Cold abscess	Puncture and drainage	
Corner[19] (1904)	1	9 F.	None	Cold abscess; miliary tubercles	Incision and drainage	Thyroid insufficiency after operation; death from miliary tuberculosis
Lediard[48] (1905)	1	21 M.	None	Tuberculous granulations with giant cells	Thyroidectomy	
v. Schiller[70] (1908)	1	17 M.	Lungs	Cold abscess; bacilli of tuberculosis found	Incision and drainage	Produced tracheal compression
Ruppanner[69] (1908)	3	30 F.	None	Tuberculosis	Thyroidectomy	
		28 F.	Scrofula as child	Caseous tuberculosis in adenoma	Thyroidectomy	Tracheal compression caused intervention
		50 F.	None	Adenoma with Basedow's stroma and caseating tuberculosis	Thyroidectomy	Signs of hyperthyroidism at forty-two
Lenormant[49] (1908)	1	40 M.	Trochanter	Caseous tuberculosis with abscess	Curettage and drainage	
Halstead[33] (1910)	1	28 F.	None	Caseous tuberculosis with abscess	Curettage	Tissue for examination obtained after spontaneous rupture
Creite[22] (1912)	2	43 F.	None	Tuberculosis; numerous tubercles	Thyroidectomy	
		58 F.	None	Tuberculous granulations without caseation	Thyroidectomy	Caused dyspnœa and dysphagia

Pollag[59] (1913)	3	58 F.		Adenoma with caseating tuberculosis	Thyroidectomy	Dysphagia prominent
		59 F.	Knee	Tuberculous caseation with abscess	Thyroidectomy	Followed amputation of knee for tuberculosis
		74 F.	None	Cold abscess	Drainage	Pressure symptoms prominent
Camera[13] (1912)	1	51 F.	None	Adenoma with tuberculous caseation	Attempted excision	Operative death
Tixier and Savy[75] (1913)	1	46 F.	None	Tuberculous granulations	Partial excision	Three weeks after operation dyspnœa developed; death; no necropsy
Arnd[3] (1912)	3	53 F.	None	Adenomatous goitre with caseation	Thyroidectomy	
		32 M.	None	Colloid goitre with tuberculosis	Thyroidectomy	
		35 F.	None	Colloid goitre with tubercles	Thyroidectomy	
Uemura[78] (1917)	24	20 F. 4 M.*	None	Adenomatous goitre with tuberculosis	Thyroidectomy	
	3	57 F.	None	Basedow's struma with miliary tubercles	Thyroidectomy	Lesion found from examination of 1,400 thyroid glands after thyroidectomy
		20 F.	None	Basedow's struma with miliary tubercles	Thyroidectomy	
		33 F.	None	Basedow's struma with moderate caseation	Thyroidectomy	
	3	39 F.	None	Tuberculous granulations	Tracheotomy	
		46 M.	None	Tuberculosis	Thyroidectomy	
		43 F.	None	Moderate caseation	Thyroidectomy	
Mosiman[55] (1917)	9	23 M.	None	Hyperplasia and tuberculosis; conglomerate tubercles	Thyroidectomy	
		29 F.	History of pleurisy	Colloid and adenomatous goitre with tubercles	Thyroidectomy	
		18 F.	None	Hyperplasia and many tubercles	Thyroidectomy	Signs of hyperthyroidism in seven cases
		60 F.	None	Sarcoma and tubercles	Thyroidectomy	
		25 F.	None	Hyperplasia and tubercles	Thyroidectomy	
		24 F.	History of pleurisy	Hyperplasia and miliary tubercles	Thyroidectomy	

TABLE I (*Continued*)

Author, Year	Cases	Age, Years and Sex	Evidence of Tuberculosis Elsewhere	Description of Process in Thyroid Gland	Treatment	Comment
		38 F.	History of pleurisy	Adenomatous goitre and considerable tuberculosis	Thyroidectomy	
		47 F.	None	Colloid goitre with tubercles	Thyroidectomy	
		32 F.	None	Hyperplasia, adenomas, and tuberculosis	Thyroidectomy	
Plummer and Broders[58] (1920)	7	33 F.	None	Scattered cases of tuberculosis and marked parenchymatous hypertrophy	Thyroidectomy	High degree of hyperthyroidism, basal metabolic rate +48, +87 respectively
		30 F.	None	Scattered cases of tuberculosis and marked parenchymatous hypertrophy	Thyroidectomy	
		44 F.	None	Extensive tuberculosis; slight parenchymatous hypertrophy	Thyroidectomy	Moderate hyperthyroidism, basal metabolic rate +26
		53 F.	None	Extensive tuberculosis; slight parenchymatous hypertrophy	Thyroidectomy	Hyperthyroidism mild or absent
		46 F.	None	Extensive tuberculosis; slight parenchymatous hypertrophy	Thyroidectomy	
		37 M.	None	Tuberculous destruction and moderate parenchymatous hypertrophy	Thyroidectomy	
		55 F.	None	Extensive tuberculous destruction of gland	Thyroidectomy	
Rendleman and Marker[64] (1921)	1	22 F.	None	Diffuse non-caseating tuberculosis	Thyroidectomy	Myxœdema post-operatively; required thyroid extract daily
Nather[56] (1921)	5	14 F.	None	Tubercles in parenchymatous gland containing colloid	Thyroidectomy	Arbitrarily classified tuberculosis of thyroid as due to:
			None	Caseation in colloid gland	Thyroidectomy	(1) tuberculous bacillæmia (2) typho-bacillosis (3) acute miliary tuberculosis
		16 M.	None	Colloid goitre with miliary tubercles	Thyroidectomy	
		26 F.	None	Colloid goitre with miliary tubercles	Thyroidectomy	

		17 M.	None	Miliary and caseous confluent tubercles in parenchymatous gland	Thyroidectomy	
Borri[10] (1924)	1		Lungs (?)	Tuberculosis	Thyroidectomy	Correct diagnosis suspected before operation
Aubriot[5] (1925)	1	52 F.	Lungs (?)	Tuberculous granulations with caseation	Thyroidectomy	
Jean[41] (1926)	1	42 M.	None	Cold abscess	Incision and drainage	Spontaneous healing of sinus
Coller and Huggins[18] (1926)	5	24 F.	None	Adenomatous goitre with considerable caseation	Thyroidectomy	
		42 F.	None	Colloid goitre with miliary tubercles	Thyroidectomy	
		38 F.	None	Miliary tubercles in exophthalmic goitre	Thyroidectomy	Compound solution of iodine had been given
		29 F.	None	Adenomatous goitre with miliary tubercles	Thyroidectomy	
		52 F.	None	Miliary tubercles in exophthalmic goitre	Thyroidectomy	Compound solution of iodine had been given
Higgins[38] (1926)	5	20 F.	None	Moderate hyperplasia with miliary tubercles	Thyroidectomy	
		30 F.	None	Tuberculosis	Thyroidectomy	Hyperthyroidism diagnosed in four cases
		36 F.	None	Areas of hyperplasia with diffuse interstitial tuberculosis	Thyroidectomy	
		46 F.	None	Hyperplasia and tuberculosis	Thyroidectomy	
		41 F.	None	Tuberculosis	Thyroidectomy	
Smith and Leech[74] (1928)	3	39 F.	None	Diffuse parenchymatous hypertrophy miliary tubercles	Thyroidectomy	
		46 F.	None	Chronic tuberculous thyroiditis	Thyroidectomy	
		36 F.	None	Tuberculous thyroiditis	Thyroidectomy	
Marcuse[52] (1928)	2	45 F.	None	Caseation with marked destruction	Thyroidectomy	
		55 F.	None	Colloid goitre with miliary tubercles	Thyroidectomy	
Frassi[30] (1929)	3	41 F.	None	Tuberculosis	Thyroidectomy	

* Average age of twenty women, 32.4 years.
Average age of four men, 27.5 years.

TABLE I (*Continued*)

Author, Year	Cases	Age, Years and Sex	Evidence of Tuberculosis Elsewhere	Description of Process in Thyroid Gland	Treatment	Comment
		9	None	Tuberculous caseation	Thyroidectomy	
		65 F.	None	Tuberculosis	Thyroidectomy	
Kipp[44] (1929)	1	45 F.	None	Adenomatous goitre with many giant cells	Thyroidectomy	Marked hyperthyroidism; basal metabolic rate +91
Villata[79] (1929)	1	62 F.	None	Tuberculosis	Thyroidectomy	
Frederiksen and Portman[31] (1929)	1		None	Adenomatous goitre with miliary tubercles	Thyroidectomy	
Budd and Williams[12] (1929)	2	42 F.	None	Sclerosing tuberculosis	Thyroidectomy	
Krafft[45] (1929)	1	43 F.	None	Sclerosing tuberculosis	Thyroidectomy	Also had diabetes
		60 F.	None	Tuberculous thyroiditis with giant cells	Thyroidectomy	Paralysis of recurrent nerve prior to operation
Hofhauser[39] (1930)	1	32 F.		Basedow's struma with miliary tubercles	Thyroidectomy	Moderate hyperthyroidism; basal metabolic rate +26
Meyer[53] (1931)	1	37 F.	Lung	Tuberculous thyroiditis in nodular colloid gland	Thyroidectomy	Sanatorium after operation, prognosis good

spontaneous rupture of a cold abscess externally. There were three cases of unilateral recurrent paralysis of nerves prior to operation. Carcinoma of the thyroid gland was diagnosed in each case because of the prevalence of this sign in cases of malignancy. A diagnosis of tuberculosis of the gland prior to operation, or even before a microscopical examination of the thyroid tissue was made, was recorded only twice. From a microscopical study of the tissues removed in the 104 cases the following conditions were reported: Tuberculosis of the thyroid gland, forty-four cases; miliary tubercles, thirty-four cases; tuberculous caseation, seventeen cases, and sclerosing tuberculosis, two cases. Tuberculous abscess was recorded six times. In seventy-two of the 104 cases the tuberculous process was stated to have been found in a colloid, adenomatous, or hypertrophic parenchymatous goitre, occurring five, forty-four and twenty-three times, respectively. On one occasion tuberculosis was associated with sarcoma.

TABLE II

*Age Incidence of Tuberculosis of the Thyroid Gland in Decades**

Sex	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79
Women...	1	4	18	31	25	15	5	2
Men.....	1	2	4	3	3			

* Represents 103 reported cases in the literature together with our twenty-one cases.

CASES FROM THE MAYO CLINIC

Since the report by Plummer and Broders,[58] in 1920, of all clinical cases of tuberculosis of the thyroid gland in which operation was performed at The Mayo Clinic up to that time, twenty-one additional cases have come to operation. A careful statistical study of the symptoms and signs which in most instances had been recorded in minute detail on special goitre history forms was made of each case. Moreover, microscopical sections of specimens of tissue removed at operation were rechecked in order to confirm the original diagnosis. A few of the more significant figures taken from the tabulated data are presented in Table III. In this manner, we hoped to establish a syndrome of symptoms at least characteristic of the condition, if not pathognomonic. A correlation of these data, however, failed to furnish a criterion by which such a clinical diagnosis could be made. Tuberculous thyroiditis was diagnosed only once, and in this instance the clinical picture was indistinguishable from thyroiditis from other causes except that leucopenia was associated with a slight elevation of the temperature. Although this form of tuberculous involvement may occasionally be diagnosed correctly prior to operation, it is well to note that in only four of our cases did the inflammatory process suggest thyroiditis and in only one case was tuberculosis suggested. Of the remaining seventeen cases, twelve were diagnosed exophthalmic goitre (the pathologist reported a hypertrophic parenchymatous goitre as well as tuberculosis in eight of these), four were considered adenomatous goitres, with or without hyperthyroidism, and one

TABLE III

*Clinical Cases of Tuberculosis of the Thyroid Gland for Which Thyroidectomy Was Performed at The Mayo Clinic**

Case	Age, Years and Sex	Chief Complaints	Clinical Evidence of Hyperthyroidism, Grade	Maximal Temperature Prior to Operation	Basal Metabolic Rate	Diagnosis	Pathological Description of Thyroid Tissue	Comment
1	53 F.	Goitre, nervousness	3	Normal	+66	Toxic adenoma	Diffuse tuberculosis in adenoma of thyroid gland	
2	44 M.	Pain, soreness in neck, fever	2	99.6	+31	Tuberculous thyroiditis	Diffuse tuberculous thyroiditis with marked fibrosis	Myxœdema five weeks after operation; thyroid extract daily; well for eight years after operation
3	41 F.	General malaise	0	99.4	+ 8	Thyroiditis	Diffuse tuberculous thyroiditis with moderate fibrosis	Well five years after operation
4	30 F.	Increasing nervousness	2	Normal	+25	Exophthalmic goitre	Diffuse miliary tuberculosis in hypertrophic parenchymatous thyroid gland	Well six years after operation
5	19 F.	Extreme irritability, diarrhœa	4	99.6	+76	Exophthalmic goitre	Diffuse miliary tuberculosis in hypertrophic parenchymatous and colloid goitre	Well five years after operation
6	49 F.	Nervousness, weakness	2	Normal	+20	Exophthalmic goitre	Diffuse marked tuberculous thyroiditis in hypertrophic parenchymatous goitre	Well three years after operation
7	49 F.	Weakness, loss of weight, nervousness	2	Normal	+51	Toxic adenoma	Diffuse tuberculous thyroiditis in marked adenomatous goitre	Well five years after operation
8	49 F.	Extreme nervousness	3	Normal	+30†	Exophthalmic goitre; cancer of breast	Diffuse tuberculosis in a hypertrophic parenchymatous and colloid goitre	Well four years after operation
9	53 F.	Loss of weight and strength	2	Normal	+10†	Exophthalmic goitre	Diffuse tuberculosis in adenoma and hypertrophic parenchymatous goitre	Well sixteen months after operation

10	37 F.	Heart trouble, goitre	1	99.8	+29†	Exophthalmic goitre; endocarditis	Colloid goitre with a few miliary tubercles; giant cells	Died three years after operation from heart failure
11	43 F.	Loss of weight, weak, nervous	2	99.4	+49†	Exophthalmic goitre	Diffuse tuberculosis with fibrosis marked; areas of caseation	Well thirteen months after operation
12	36 F.	Palpitation, nervousness	2	99.8	+30	Exophthalmic goitre	Tuberculosis in a hypertrophic parenchymatous and colloid goitre	Well fifteen months after operation
13	39 F.	Pain and tenderness in neck	0	100.0	− 2	Thyroiditis	Diffuse tuberculous thyroiditis with moderate fibrosis	Well seventeen months after operation
14	25 F.	Goitre	0	99.4	− 7	Non-toxic adenoma	Diffuse tuberculosis in an adenomatous goitre	
15	68 F.	Palpitation, nervousness	2	99.6	+42†	Exophthalmic goitre	Colloid and fetal adenoma with miliary tubercles	Considerably improved after eight months
16	59 M.	Nervousness, loss of weight and strength	2	99.6	+33†	Exophthalmic goitre	Diffuse tuberculosis in hypertrophic parenchymatous and colloid goitre	Well at present time
17	70 F.	Palpitation, nervousness, weakness	2	Normal	+19	Toxic adenoma	Diffuse tuberculosis in adenomatous goitre	Well at present time thirteen months after operation
18	54 F.	Goitre, dysphagia	0	100.4	+ 8	Thyroiditis	Diffuse tuberculosis in adenomatous goitre	Well at present time eighteen months after operation
19	37 F.	Marked nervousness and loss of weight	3	Normal	+42†	Exophthalmic goitre	Tuberculosis in a colloid and fetal adenomatous goitre	Died after leaving hospital, of pulmonary embolus
20	42 F.	Rapid growth of tumor of neck	0	Normal	None	Hæmorrhagic cyst of thyroid gland	Diffuse tuberculous thyroiditis limited to isthmus	Well at present time eleven months after operation
21	48 F.	Palpitation, weakness, loss of 50 pounds	2	Normal	+22	Exophthalmic goitre in adenomatous goitre	Diffuse tuberculosis in adenomatous and hypertrophic parenchymatous goitre with colloid	Gall-bladder removed eight months later; well at present time

* In no instance was there a suggestive history of tuberculosis elsewhere in the body nor was such evidence noted on examination prior to operation or at subsequent examination.

† Patient had been taking iodine prior to test.

case was diagnosed hæmorrhagic cyst of the isthmus, because of its sudden onset and rapid increase in size. The clinical syndrome of hyperthyroidism, manifested by increased nervousness and irritability, progressive loss of weight and strength notwithstanding increased appetite and consumption of food, and intolerance to heat, was the outstanding feature in all but five cases. The examining clinician, on the basis of his observation and the laboratory data, classified the cases as follows: a high degree of hyperthyroidism, five cases (Cases I, V, VIII, XV, and XIX, Table III); moderate degree of hyperthyroidism, ten cases (Cases II, IV, VI, VII, IX, XI, XII, XVI, XVII, and XXI, Table III), and little if any hyperthyroidism, six cases (Cases III, X, XIII, XIV, XVIII, and XX, Table III). The basal metabolic rate was + 19 per cent., or more in fifteen cases, + 10 per cent., or less in five, and not obtained in one case. Five patients, four of whom were in the larger group, had been taking compound solution of iodine prior to the metabolism test.

Each patient in this series was subjected to a careful examination before and following operation to determine if there was evidence elsewhere in the body of tuberculosis, particularly in the lungs. In no case, however, was there either röntgenological or clinical evidence of such involvement. During the pre-operative period an elevation in temperature (acute infection of the respiratory tract was ruled out in each instance) between 99.4° and 100.4° F. was noted in eleven cases on more than one occasion.

There were two men and nineteen women in our series. The average age of the men was fifty-one years, and of the women 44.3 years. The ages according to decades in our cases and in those from the literature are shown in Table II. Fifty-four per cent. of the patients were between the ages of thirty and forty-nine years, being almost equally distributed in the fourth and fifth decades.

The pathologists based their diagnosis in our cases on the findings of the characteristic tubercles within which were found one or more giant cells. The tuberculous process was diffuse in seventeen cases, many tubercles being found in most instances as well as an abundance of giant cells. In only one instance was a prolonged search necessary in order to isolate the characteristic evidences of tuberculosis. Considerable fibrosis was noted in six cases, five of which represented pure thyroiditis unassociated with adenomatous or hypertrophic changes; one case was associated with multiple adenomas.

Noticeable difference from other cases of goitre was not observed during convalescence from thyroidectomy with the exception that in about five of the tuberculous cases there was profuse drainage from the wound of a clear watery material which persisted over a period of one to two months. Two-thirds to three-fourths of the thyroid tissue was removed in 70 per cent. of the cases; in four cases the surgeon stated that because of the marked thyroiditis only about half of the tissue was removed since it was feared that the removal of a greater quantity would result in myxœdema. Thyroid insufficiency as manifested by myxœdema developed in only one case, and

this patient was one of the group of four in which special precaution was taken to prevent just such occurrence. It would appear that, since thyroid insufficiency has been noted in only three of 125 reported surgical cases (thyroidectomy in 115), under ordinary circumstances the same amount of gland may be removed in tuberculosis as in uncomplicated exophthalmic and adenomatous goitre. The thyroid insufficiency in our case and in the two cases reported in the literature was readily corrected by the administration of thyroid extract. In our case myxœdema developed five weeks after operation and for eight years the patient has taken thyroid extract daily. His general condition is excellent. There was but one death; the patient died from a pulmonary embolus on the twelfth post-operative day, after having been dismissed from the hospital in apparently good condition.

Two patients have not been heard from since operation. Five were living and well five or more years after operation, and the remainder have been communicated with or reëxamined recently. None has shown evidence of continuation of the tuberculous process or the hyperthyroid state. Judging from our observations, and from similar data reported in the literature, the prognosis in such cases is highly satisfactory.

Etiology.—The manner of origin of tuberculosis of the thyroid gland remains obscure. Although it was impossible to locate a focus of tuberculosis outside the gland in any of our cases, and in only a few of those reported in the literature, nevertheless it is probable that all such cases are secondary to some process elsewhere in the body too small to have any clinical significance. It appears remarkable, however, that in approximately 114 clinical cases the thyroid gland should apparently alone become invaded from a primary focus. This is all the more unique when we consider the relative immunity of this structure to tuberculous involvement with the fact that any invasion other than by continuity, must be by the blood-stream since retrograde flow of lymph into the thyroid gland is not possible, due to the potent valves interspersed along these channels. In other words, in such cases the thyroid gland must become invaded as the result of tuberculous bacillæmia. These patients must, it would appear, enjoy a high degree of general immunity to the bacillus of tuberculosis, else fatal generalized miliary tuberculosis would develop. This may explain why, in most of the cases observed after partial thyroidectomy, the patient completely recovers and at least for a number of years shows no evidence either of thyroid dysfunction or of tuberculosis.

The specific microscopical changes peculiar to tuberculosis have been produced experimentally in the thyroid glands of animals by Roger and Garnier,[67] Torri,[77] Tomellini,[78] Shimodiara[78] and others. Roger and Garnier, using guinea-pigs and rabbits, injected emulsions of the bacillus of tuberculosis into the carotid artery. Torri, employing dogs, made similar injections into the thyroid artery. He concluded that the colloid material in the glands possesses a bactericidal action for the bacillus of tuberculosis since he could not recover bacilli from the colloid of the glands ten days after injection. He further demonstrated that the bacilli became attenuated, after prolonged contact with colloid from goitres of human beings. Tomellini, in a similar manner, experimented

with rabbits. Experiments conducted by Shimodiara are of particular interest in that they probably represent, as Arnd[3] has stated, more nearly the true relation of the thyroid gland to tuberculous infection. He employed a constant emulsion of the bacillus of tuberculosis which he injected intravenously into rabbits in decreasing concentrations in such a manner that dilutions which produced tuberculous infection of the thyroid gland, spleen, kidney, and testis, would on further dilution continue to produce the specific lesions in the spleen, kidney and testis but not in the thyroid gland. Arnd believed that these observations, correlated with the comparative scarcity of tuberculosis of the thyroid gland of human beings, denote a relative immunity of the gland to the bacillus of tuberculosis. Moreover, since in acute miliary tuberculosis the infection is so overwhelming, he is of the opinion that the thyroid gland along with other organs is of necessity involved because of the massive invasion. Such infections, therefore, are not significant in determining the relative susceptibility of the gland to tuberculous infection. More recently, Nather, Gloyne,[22] and others have shown that the substance of the thyroid gland of human beings, as well as of various animals, has no bactericidal effect on the bacillus of tuberculosis *in vitro*. Nor does thyroid gland administered to experimentally infected animals over a course of several weeks arrest the disease.

Gloyne found little evidence for supposing that the thyroid gland itself has any direct antitoxic action in tuberculosis. He suggests that it is possible there is some anatomical reason that the gland so frequently escapes infection, and cites the heart and voluntary muscle as similar examples of this relative immunity.

Plummer and Broders are of the opinion that the relationship between hyperthyroidism and tuberculosis of the thyroid gland is not a coincidence. They stated: "Either a hypertrophic gland is rendered more susceptible to invasion by the bacillus of tuberculosis or the infection stimulates the parenchyma to abnormal activity and is thus indirectly responsible for the hyperthyroidism with its attendant symptoms. Although the great majority of hypertrophic thyroid glands are not tuberculous, any infection which may even in a few instances be an etiologic factor is of interest in dealing with a disease the cause of which is so shrouded in mystery." As far back as 1905 Costa, and later Dumas, and Hufnagel, suggested that exophthalmic goitre represents a tuberculous process in the thyroid gland. Uemura,[78] in 1917, again raised the question in regard to the relationship between tuberculosis and the genesis of exophthalmic goitre. Mosiman,[55] the same year, brought out the striking association between hyperthyroidism and tuberculosis of the thyroid gland. Plummer and Broders, in 1920, further stressed this association and reported hyperthyroidism in five of their seven cases. On the other hand, Coller and Huggins,[18] in 1926, stated their belief that the view that tuberculosis stimulates the gland to abnormal activity is untenable. This opinion was based on a study of one of their cases, which apparently indicated that there was no appreciable effect on the parenchymatous hypertrophy or its activity by the development of miliary tubercles in the gland, and because the parenchyma of the experimental tuberculous glands in animals was not stimulated to a hyperplastic state. There have been instances, however, in which such changes have been noted in experimental animals, notably in the experiments conducted by de Quervain, and which have been considered elsewhere. These authors are inclined to believe that the presence of tuberculosis in the hyperplastic type of gland is a coincidence. In fifteen of our twenty-one cases there were clean-cut evidences of hyperthyroidism, and in eight cases there was simultaneous microscopical evidence of tuberculosis and parenchymatous hyperplasia, yet it was impossible for us to reach a definite conclusion in regard to whether the tuberculosis preceded the hyperthyroidism and the hyperplasia or if the converse was true.

A distinction must be made between tuberculous infection of the thyroid gland and the so-called sclerosing tuberculosis of the French authors, which is said to occur secondarily to pulmonary tuberculosis. There is practically

nothing known of the pathological changes in the thyroid gland in the early stages of pulmonary tuberculosis, since thyroidectomy was seldom done during this period. Yet it is in this early stage that symptoms of thyroid disturbances are most commonly encountered. On the other hand, there is an abundance of necropsy evidence, chiefly in the French literature, of the occurrence of marked sclerosis in the thyroid glands of patients who died from pulmonary involvement. It is generally agreed that this type of lesion is a consequence of toxæmia, incident to advanced pulmonary tuberculosis rather than to a bacillary invasion. Further evidence that the process is not a direct result of the bacillus of tuberculosis is the lack of characteristic histological evidence of tuberculosis and the failure of investigators to recover the organisms from such glands. The sclerosis described by Budd and Williams,[12] in which typical tubercles containing giant cells were observed, is an entirely different condition. We encountered this form of reaction to the direct invasion of the gland by the bacillus on several occasions.

Pathology.—A diffuse miliary process was the most common observation in our cases; this form was diagnosed microscopically in seventeen cases. (Figs. 1 to 7.) It is likewise the most common form reported in the literature. A distinction must be made between miliary involvement of the thyroid gland as part of a generalized fatal tuberculosis in which all the organs are more or less riddled with tubercles, and a similar process in which there is also tuberculous bacillæmia, but in which the disease localizes in the thyroid gland without fatal outcome. The tubercles in the thyroid gland are not dissimilar to tubercles in other organs. They have been described as being interacinar and intra-acinar, the former occurrence being more common. We noted both forms as well as a combination of the two. An abundance of giant cells is the rule although it may be difficult or impossible to find them. This is particularly true when there is a tendency toward healing within the tubercles. This tendency is probably more common than the tendency toward progression of the disease. We have noted various stages of the healing of tubercles in glands which also showed areas in which the tubercles revealed no evidences of healing. Less frequently conglomerate tubercles are encountered which evidently have formed from the union of discrete tubercles. Subsequently caseation may develop within these masses, and these in turn may eventually break down into cold abscesses. Such progression of the disease, however, is extremely rare. Still rare, but somewhat more common, is the development of considerable fibrous tissue as a reaction to the infection present within the thyroid gland. This type of gland is liable to be small and firm and will give rise clinically to a suspicion of thyroiditis or malignancy. We encountered four such glands, two of which were slightly larger than normal, whereas the other two represented normal or slightly smaller glands. In the earlier stages before most of the glandular tissue is destroyed one is likely to encounter well-formed tubercles, but as the process advances there is practically nothing remaining but firm, tightly woven fibrous tissue in which an occasional tubercle or giant cell

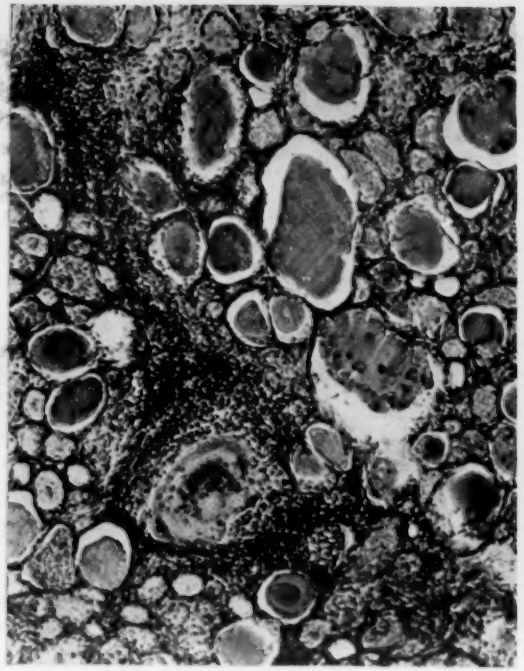

FIG. 1.

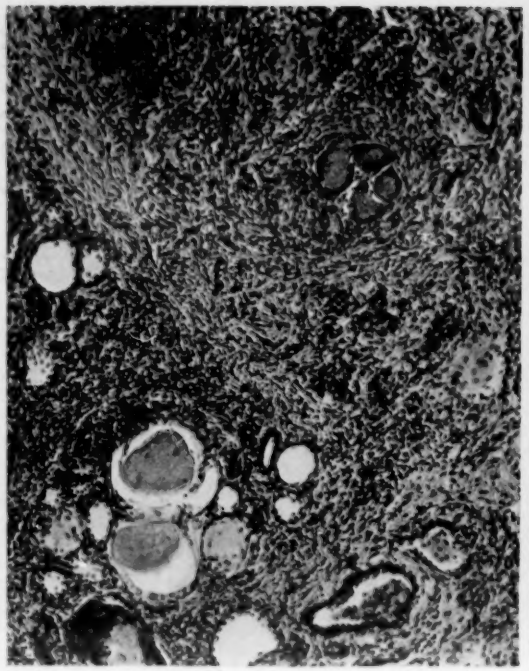

FIG. 2.

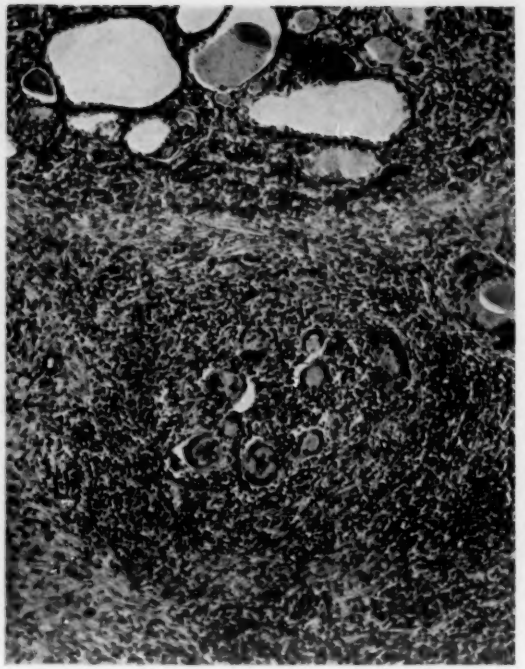

FIG. 3.

FIG. 1.—Early diffuse tuberculous thyroiditis of the isthmus in a colloid thyroid gland; multiple tubercles with many large giant cells; marked round-cell infiltration.
FIG. 2.—Diffuse tuberculous thyroiditis; tubercles with many giant cells and moderate fibrosis.
FIG. 3.—Diffuse miliary tuberculosis in colloid thyroid gland; tubercle containing many giant cells; moderate fibrosis and round-cell infiltration.

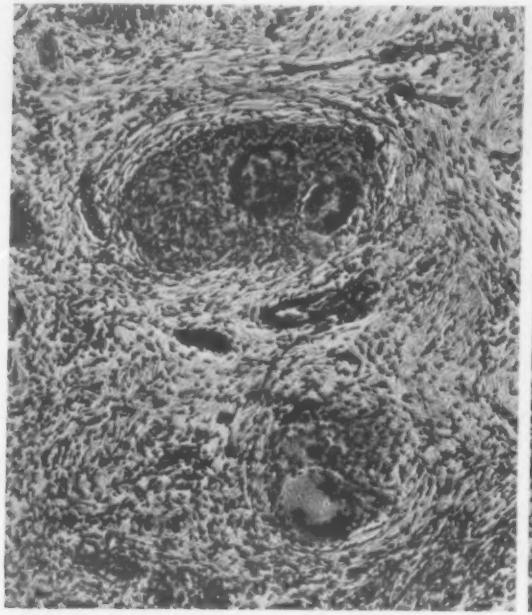

FIG. 4.

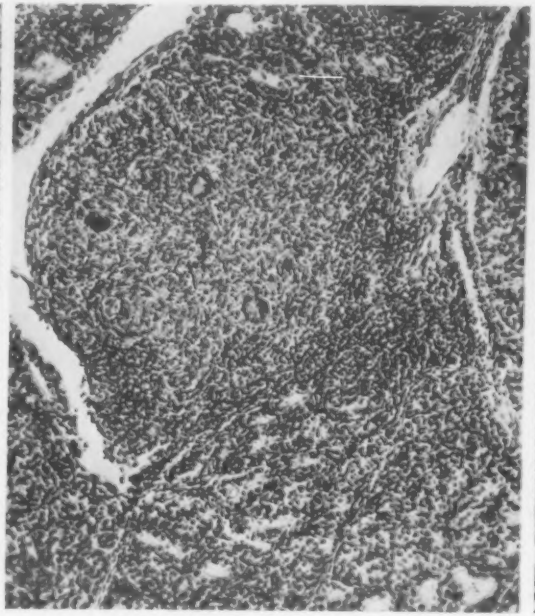

FIG. 5.

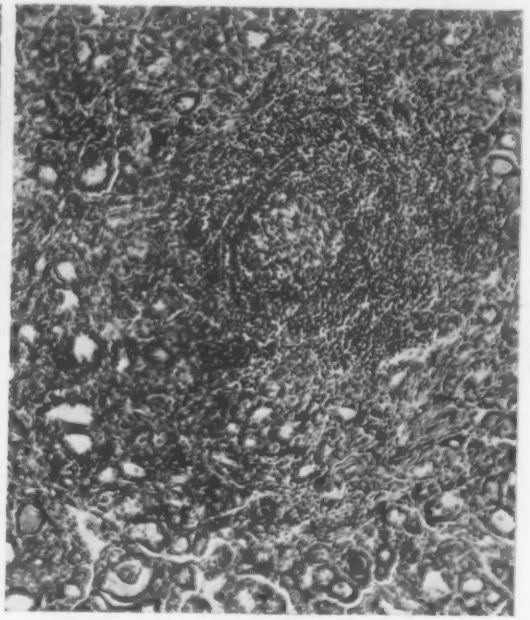

FIG. 6.

FIG. 4.—Diffuse miliary tuberculosis in an adenomatous thyroid gland; fibrosis marked. Very little gland tissue remains.
FIG. 5.—Diffuse miliary tuberculosis in a hypertrophic parenchymatous thyroid gland; tubercle containing numerous small giant cells.
FIG. 6.—Diffuse miliary tuberculosis in an adenomatous and hypertrophic parenchymatous thyroid gland; multiple areas of necrosis with but few giant cells.

may be discerned. (Fig. 4.) Each form of lesion as depicted here probably represents a progressive stage in the development of a single process which begins as one or more discrete miliary tubercles, and, depending on the natural or acquired resistance of the individual and the virulence of the organism, there is either a tendency toward healing or else toward progression of the disease which may stop at any stage or go on to the formation of abscess.

An entirely different type of lesion is the sclerosing tuberculosis mentioned by French authors which has been considered elsewhere. This condition is thought to be due to the presence in the blood-stream of tuberculous toxins in cases of advanced pulmonary involvement. The specific lesion caused by bacillus of tuberculosis is never found, nor has anyone ever been

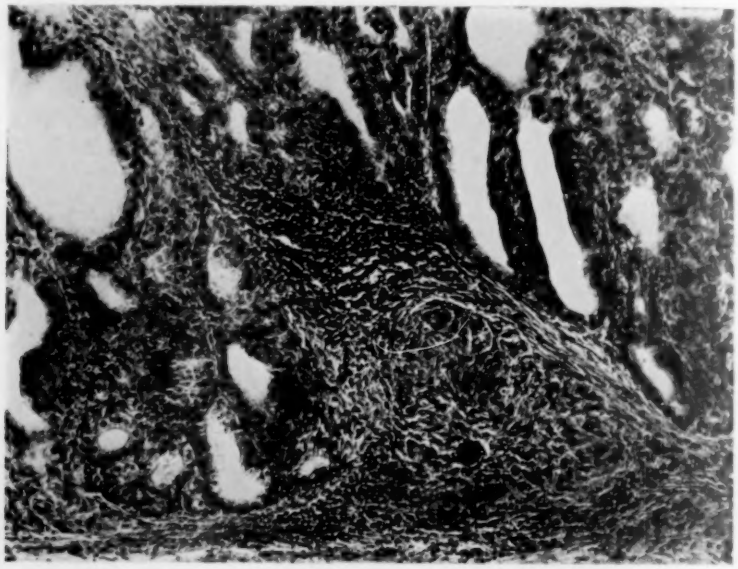

FIG. 7.—Tuberculosis in an adenomatous thyroid gland; tubercle containing an enormous giant cell.

able to isolate the bacillus itself in such cases. Failure to demonstrate bacillus of tuberculosis in the tissue has not in the past prevented a diagnosis of tuberculosis of the thyroid gland if the histological picture was characteristic. Hedinger[35] was particularly successful in his ability to demonstrate the organism in tissue, noting them in nine of ten cases. He was in agreement, however, with Lediard,[48] Ruppanner,[69] Corner,[19] Halstead,[33] Arnd and others who felt that a satisfactory diagnosis could be made from the histological picture. Mosiman, and Plummer and Broders, and most of the subsequent investigators have continued to accept the histological evidence as the diagnostic criterion.

SUMMARY AND CONCLUSIONS

Tuberculosis of the thyroid gland has been considered historically and statistically. Although reports of involvement of the thyroid gland demon-

strated at necropsy following deaths from general miliary tuberculosis are of academic value, we have confined our statistical study to clinical cases. The incidence of clinical tuberculosis of the thyroid gland has been shown to be extremely low; in the course of microscopical study of 20,758 thyroid glands removed surgically at The Mayo Clinic over a period of eleven years, tuberculosis was diagnosed in twenty-one, an incidence of approximately 0.1 per cent.

One hundred four cases of surgically treated tuberculosis of the thyroid gland reported in the literature, and twenty-one cases from The Mayo Clinic were tabulated separately. The combined data revealed a marked predominance of women patients evenly distributed over the fourth and fifth decades. Although evidence of active tuberculosis was present in only six of 125 cases and suspected in five others, the prevailing opinion is that probably all cases are secondary to some disease process elsewhere in the body. Diagnosis prior to microscopical study of tissue removed at operation is extremely rare; only three such instances are recorded. It was impossible from a detailed study of our data on twenty-one cases to determine criteria by which a clinical diagnosis could be made. The principal syndrome exhibited by these patients was that of hyperthyroidism, which was noted in fifteen cases, with an increased basal metabolic rate of +19 per cent. or higher. Moreover, the question of whether the hypertrophic gland is rendered more susceptible to invasion by the bacillus of tuberculosis or the infection stimulates the parenchyma to abnormal activity, and is thus indirectly responsible for the hyperthyroidism, could not be conclusively determined.

Evidence of thyroid deficiency was noted after thyroidectomy in only three of 115 cases. Diffuse miliary tuberculosis, in which there were typical epithelioid tubercles and giant cells, was by far the most common observation; caseation was reported in about a fifth of the cases studied; abscess, and evidences of marked sclerosis, were less frequently noted. Tuberculosis occurred in an adenomatous goitre in fifty-one cases, in a hypertrophic parenchymatous gland in thirty-one cases, and in a colloid gland in six cases. Convalescence after thyroidectomy in these cases was not different from that of cases of uncomplicated adenomatous or exophthalmic goitre, and, as in these, the same excellent prognosis can be given.

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Discussion.—Dr. Martin B. Tinker (Ithaca, N. Y.) said that Doctor Rankin's paper had brought out points that have come in the experience of most surgeons who have had similar cases: First, that the diagnosis of tuberculosis of the thyroid is difficult but not impossible before operation; second, that on the operating table appearances are more likely to suggest simple thyroiditis, rather than tuberculosis; and third, that these cases are quite readily curable.

In certain instances the condition may be of great gravity: his first case, diagnosed by Doctor Bloodgood, of Johns Hopkins, as "tuberculosis of the thyroid," came on a stretcher in rather a precarious condition. He was a physician then practicing in Little Falls, New York, but is now President of a State Medical Society in the Southwest, where he went for his health after recovery from his operation. His extreme prostration was apparently attributable to the thyroid condition, not tuberculosis which affected simultaneously other organs of the body, for he recovered promptly after thyroidectomy, is now perfectly well and doing a large practice.

A certain number of these patients need much the same rest, dietetic and climatic treatment advised for patients with tuberculosis of other organs of the body.

Dr. Alexis V. Moschcowitz (New York City) said that his experience with this variant of tuberculosis or this form of thyroiditis is limited to two cases. One of these is particularly interesting. A man on a visit to New York City was suddenly taken acutely ill with a very high temperature. He was seen in consultation by a number of physicians. The outstanding features of his illness were a swelling of the right lobe of the thyroid gland and hyperpyrexia up to 106°F. When seen by Doctor Moschcowitz, the physical signs and symptoms above-mentioned were still present. He therefore diagnosticated a deep suppurative thyroiditis and advised urgent operation. Preliminary

aspiration failed, however, to reveal the presence of pus. Because of the pressure upon the trachea, operation was proceeded with. Exposure of the right lobe of the thyroid gland showed it to be exceedingly hard, typical of a Riedel's eisenharte Struma. The greater portion of the right lobe of the thyroid gland was excised piecemeal and practically without any bleeding; the patient made an uninterrupted recovery. Doctor Mandelbaum, pathologist to Mt. Sinai Hospital, reported the specimen as one of tuberculosis. The case healed so kindly, however, that Doctor Moschcowitz is still inclined to doubt somewhat the correctness of the pathological diagnosis.

Dr. George W. Crile (Cleveland) said that in eighty-six cases they had deliberately performed thyroidectomy in the presence of tuberculosis of the lungs on the ground that the patients had two diseases. Sufficient time has not elapsed since these operations to determine the end-results except to say that all are greatly improved. In no one of the eighty-six cases was there any tuberculosis of the thyroid gland.

Dr. John Douglas (New York City) commented on the statement of Doctor Rankin that in the after-course of his patients there was only one thing in any way characteristic, the rather profuse discharge of serum. Doctor Douglas operated on a case of tuberculosis of the thyroid about a year ago. He did not make the diagnosis before or at the operation, and the only thing which was particularly characteristic or unusual about this case was the fact that the woman had symptoms, particularly an increased metabolic rate which was out of all proportion to the size of the thyroid. She had a comparatively small gland, not adenomatous but of the hyperplastic type. If this was a toxic thyroid with such a small increase in size, it must be necessary to take out a rather large amount of the gland in order to remove the toxic symptoms. He did a rather complete subtotal thyroidectomy. To his surprise he received a report of tuberculosis of the thyroid gland. The only after-result was not a very profuse discharge of serum from the wound, but a very considerable amount of induration in the woman's neck in the region of the scar for many weeks longer than one would expect after an ordinary thyroidectomy. While she did not have a high temperature of a post-thyroidectomy form, she persisted around 101° for a long time. Most of these symptoms could be explained by the fact that it was a tuberculous infection with some absorption of the toxin following the operation. He asked whether there was a marked induration, and whether there was a prolonged high temperature in Doctor Rankin's cases.

Dr. William F. Rienhoff, Jr. (Baltimore), remarked that of course thyroiditis in this form is a chronic inflammation and one would expect a chronic inflammatory reaction in the tissues to whatever agent is producing the chronic thyroiditis. In other words, if these cases are primarily tuberculosis of the thyroid it is after all a chronic infectious process which will produce a chronic inflammatory reaction. It is only logical to assume, however, that if some other agent can be used other than the tubercle bacillus to produce a similar chronic inflammatory reaction the cytological response might be very similar to that caused by the tubercle bacillus. They have found this to be a fact and injections of paraffin and agar-agar into the thyroid glands of guinea-pigs and dogs have been followed by a cytological reaction in many ways quite similar objectively to that cytological reaction produced by the tubercle bacillus. In other words, there have been giant cells in an area surrounded by epithelioid and small round-cell infiltrations. Of course in the latter experiments the tubercle bacillus was not present and therefore one can conclude that the presence of a cellular reaction which is similar, histologically, to that seen in tuberculosis is not pathognomonic of the disease tuberculosis, and therefore, unless tubercle bacilli have been demonstrated either by staining or by putting some of the tissues in a guinea-pig with the pig developing tuberculosis later, one really cannot conclude that this type of chronic thyroiditis is tuberculous. He wondered if Doctor Rankin had, in these cases, been able to demon-

strate the tubercle bacilli. He had had similar cases in Baltimore which looked, histologically, very much like tuberculous thyroiditis but in which cases they had been unable to show, either by staining or the use of guinea-pigs, that the infection was tuberculous. He personally believed that some degenerative process which will allow the colloid to escape from the follicle into the interfollicular spaces will produce a foreign body reaction and an inflammatory reaction very similar to that produced by agar-agar and paraffin. They are at the present time attempting to prove this point. Certainly one can say that the cytological reaction seen in tuberculous lesions is not pathognomonic of the disease tuberculosis.

This controversy, as to what constitutes tuberculosis of the thyroid gland, has been going on ever since Riedel, in 1896, described chronic ideopathic thyroiditis, ligneus thyroiditis, or Riedel's struma. It has often been called tuberculosis of the thyroid gland and also carcinoma of the thyroid gland. The earlier stages of this condition of thyroiditis were described by Hashimoto, in 1912, who called this condition "struma lymphomatosa." Riedel described the late stages.

For some years there was a prolific discussion as to the etiological factors and a great many of the French observers thought this was a syphilitic thyroiditis, and others thought it was a tuberculous thyroiditis, but the specific organisms could never be demonstrated.

Dr. Fred W. Rankin, answering the question as to convalescence following thyroidectomy when tuberculosis of the thyroid has been observed, said that in their group of cases there had been no difference from the usual standardized type except for the prolonged drainage which he had mentioned. The drainage was of the profuse, watery type, which they had not noticed following thyroidectomies for other reasons. Infiltration of the wound had not been observed in any of these twenty-one cases. He should be inclined to think that it was secondary to some type of infection, such as is occasionally seen in goitre wounds following operation for hyperplastic goitre.

He thought Doctor Crile's point to be very well taken, namely, that the hyperthyroidism should be operated on in the presence of the pulmonary tuberculosis under certain conditions. They too have operated on a number of patients who had a co-existing pulmonary lesion and hyperthyroidism. The outcome of these cases he did not know in detail at present but he felt it a sound principle to eliminate a semi-acute condition in order to influence favorably the chronic pulmonary lesion.

Relative to Doctor Reinhoff's question as to whether or not they had been able to substantiate the pathological diagnosis of tuberculosis of the thyroid gland by staining specimens or by injection into guinea-pigs, they had not. Their pathologists had depended on the characteristic microscopical picture, as evidenced by the presence of epithelioid and giant cells, and had felt that this was sufficient to warrant the hypothesis of tuberculosis in the thyroid gland as a clinical entity. They had not been able to stain the specimens and obtain the tubercle bacillus and they had not tried animal injection. He thought there is unnecessary confusion about this type of diagnosis. He believed pathologists are willing to accept the diagnosis of tuberculosis of the thyroid without all of the above-mentioned data. Unquestionably, tuberculosis of other locations, such as of the kidney or spleen, is diagnosed on such a picture in certain cases, without the substantiation of guinea-pig inoculation or staining.

PARATHYROIDISM

By Max Ballin, M.D.
of Detroit, Mich.

At the meeting of the American Surgical Association in 1931 I made a communication on parathyroidism and parathyroidectomy based on about twenty-five cases of parathyroidectomies published in the literature, sixteen personal observations, and fifty autopsies in the literature where skeletal changes were found with parathyroid tumors.

These numbers have increased considerably during the year. Over fifty parathyroidectomies for osteomalacic conditions have now been published besides the seventy parathyroidectomies for ankylosing polyarthritis reported from Oppel's clinic in 1928. Our own experience has increased to forty-five cases of such operations. Numerous autopsies showing the coincidence of parathyroid tumors with osteomalacia have been added (Brines, Hartman, *et al.*). Wherever the condition becomes known, the diagnosis is made quite frequently. To my knowledge, in Detroit, where the subject of parathyroidism has been discussed a good deal, four surgeons have done parathyroidectomies. Dr. Wm. H. Gordon, of Harper Hospital, has, within the past year, diagnosed parathyroidism eight times in his private practice and in our Out-Patient Department. Dr. R. V. Funston, of the orthopædic department at Harper Hospital, has diagnosed the condition so frequently that he has sent eight cases for parathyroidectomy and considers this chapter a valuable addition to orthopædic work. From each of the cities where my colleagues, especially Dr. Plinn Morse, have read papers on the subject, we always receive X-ray films of one or more patients, and sometimes the patients themselves are sent with the condition well established. Dr. A. A. Mertz and Dr. C. H. Tearnan, of Decatur, Illinois, realized after hearing one of Doctor Morse's papers that they had four such patients, under observation a long time, without a diagnosis being made. Two of them, very advanced cases, we operated upon with striking results; and up to now they themselves have operated upon four more. It is interesting how these colleagues, as well as others, recall that they have invalid patients who have been sitting in chairs or lying in bed for years, and now on re-examination they make the diagnosis and treat the patient for parathyroidism. I have gone into this a little too elaborately, perhaps, but it seems to be simply a matter of becoming acquainted with the entity to find plenty of cases. To be sure, a larger experience is still needed to draw more definite conclusions as to the extent of the parathyroidism and the variety of symptoms to be included in the entity, and to understand better the indications for medical or surgical treatment. Our diagnostic facilities have also been very much

enhanced during the year by the addition of precise methods of determining the muscular hypotonia coincident with this affection.

Of thirty-five cases tabulated from the literature by John Helström, in 1932, thirty-three showed tumors of the parathyroid, and nearly all of them had the classical bone changes of generalized osteitis fibrosa cystica. Of our forty-five cases, only twenty-two offered the same classical picture as the outstanding symptom. This comparison of the two tabulations suggests that

FIG. 1.

FIG. 2.

FIG. 1.—G. P., a woman, fifty-four years old. Fractures of clavicle, humerus and ribs for fifteen to twenty years. Back and leg ache, limping, scoliosis, two-inch loss in height, demineralization of all bones, wedging lower dorsal and fifth lumbar vertebræ; calcium fourteen milligrams, phosphorus two and one-half milligrams. Patient very weak. Parathyroidectomy, two glands removed, adenomatous. Clinically cured.

FIG. 2.—Mrs. J. B., sixty years. Practically the same type of case as Fig. 1, sick four years. Calcium twelve milligrams, all X-ray signs, chronaxie .16/1000. Good clinical result from parathyroidectomy.

the surgeons whose operations Helström tabulated did parathyroidectomies only for the entity of generalized osteitis fibrosa cystica, and there can be no doubt that the skeletal complications of osteitis fibrosa cystica generalisata (von Recklinghausen's disease) are so far recognized as the main indications for parathyroidectomy. The symptoms are very clearly outlined now and consist in more or less general decalcification, the findings of osteitis fibrosa cystica; mottled appearance of the flat bones; cyst formation in the long bones; replacement of bony tissue by giant-cell tumors; spontaneous, multiple fractures; and curvatures and deformities of the long bones and spine.

Besides these changes the high serum calcium with lessened serum phosphorus, the negative balance in the calcium metabolism, and the increased calcinuria are classical symptoms and indications for parathyroid investigation. Figures 1 to 4, with their legends, are illustrative of a few of the nearly 100 cases published as classical findings of parathyroidism and indications of parathyroidectomy.

But less classical symptom complexes should also be taken into con-

Fig. 3.

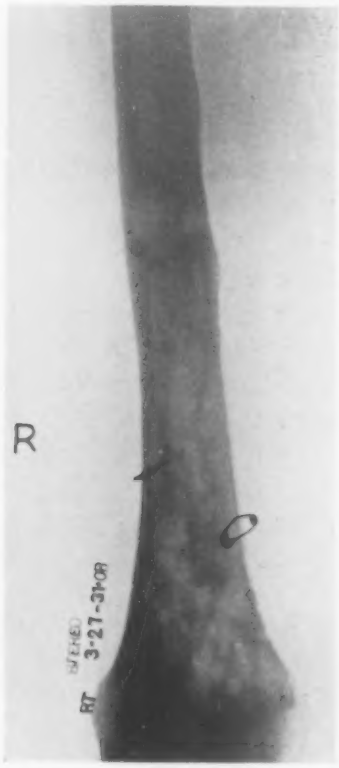


Fig. 4.

Fig. 3.—Mrs. E. W., forty-five years. The long bones in a typical case with vertebral compressions. The femur with cysts and giant-cell tumor (osteoclastoma).

Fig. 4.—Same case as Fig. 3. Small size osteoclasia, osteitis fibrosa cystica in other femur.

sideration in order to give many patients the benefit of our knowledge of parathyroidism and its medical and surgical treatment.

Besides type (1)—Classical osteitis fibrosa cystica generalisata, with vertebral compression, bone cysts, *etc.*, we will discuss (2) Paget's type, (3) arthritic type, (4) juvenile type and (5) myasthenic type.

(2) *Paget's Type.*—The question of whether Paget's disease belongs to this group and whether it can be benefited by parathyroidectomy has not as yet been settled. The opinion that Paget's disease and von Recklinghausen's disease (osteitis deformans and osteitis fibrosa cystica generalisata) are one entity is coming more and more to the front. The pathological

differentiation shows all transitory stages from one to the other. Röntgenologically, both types of the affection have been found in the same patient. D. E. Shouten, Bourguignon and Sainton, and Ballin and Morse have observed cases of osteitis fibrosa cystica with Paget's deformities. The fact that Paget's disease is followed in about 15 per cent. of the cases by sarcoma

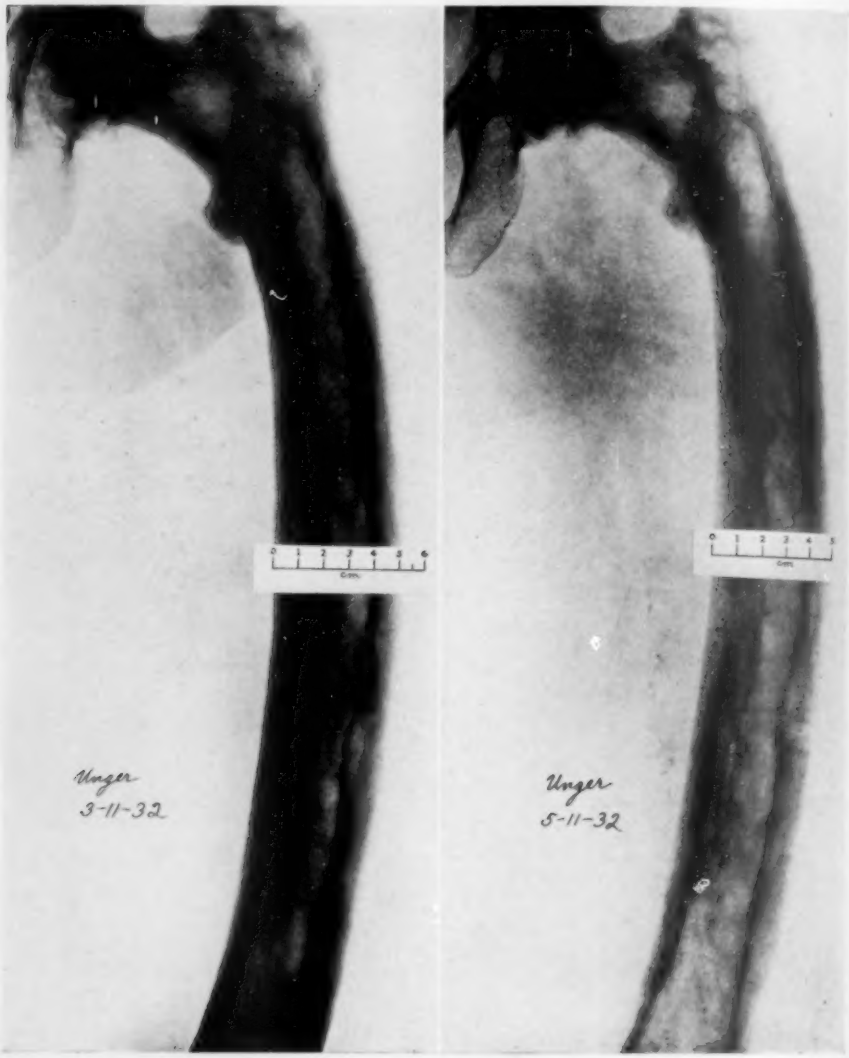


FIG. 5.—Mrs. S. B. U., sixty years old. A typical monostotic Paget's disease of the femur with some improvement beginning two months after operation.

is not differentiating. Malignancy has also followed osteitis fibrosa cystica. Benjamin F. Joseph reports a case of giant-cell sarcoma in a case of osteitis fibrosa cystica metastasizing into the inguinal lymph-nodes. A. Fromme also writes concerning the relation of osteitis fibrosa cystica to sarcoma. If we consider Paget's disease a form of osteitis fibrosa cystica occurring at

a later age, we can easily understand why sarcoma follows oftener in Paget's than in osteitis fibrosa cystica. Clinically the symptoms of osteitis fibrosa cystica and osteitis deformans merge into each other without any striking distinction being present; the former usually runs a more rapid, painful, and the latter a more chronic course. Our therapeutic experience has taught us that the symptoms of osteitis fibrosa cystica as well as those of Paget's disease have been improved by parathyroidectomy. (See also Bourguignon and Sainton, and Bovee.) Some men try to differentiate between the monostotic type of Paget's and the polyostotic form, but such distinction is just as impossible as in monostotic cysts and multiple polyostotic cystic forms of osteitis fibrosa cystica. Again both blend into each other, and in the seemingly monostotic types of both there are usually slight changes throughout the skeleton.

FIG. 6.

FIG. 7.

FIG. 6.—V. J. T., fifty-three years old. Skull in Paget's disease before parathyroidectomy. This patient had typical Paget's disease, head grew larger, deafness, weakness and pain in limbs. Two hyperplastic parathyroids removed.

FIG. 7.—Same patient as Fig. 6, six months after operation. Note how skull has improved, especially disappearance of the fuzzy, cotton-like (nigger wool) appearance of the outer table.

Our experience with Paget's type is somewhat short in duration to warrant definite statements, but encouraging enough to stimulate further study.

CASE I.—F. T., aged sixty years, typical Paget's type. Picture presented in our last year's paper showed immense skull and large, curved, thickened tibia and femurs. Parathyroidectomy, June 24, 1931. Blood serum calcium 11.6 milligrams. Immediately after the operation the pain in his extremities was relieved to such an extent that he could walk again and become an office patient, which had been impossible for him for many months. He died, however, from cerebral symptoms, pressure on cranial nerves caused by sarcomatous changes in his Paget's skull.

CASE II.—Mrs. S. B. U. clinically had a monostotic type of Paget's disease of the femur of several years' standing. Lately there has been a good deal of pain in the limbs and back. Besides the Paget's findings there was some arthritic process. This woman had a marked parathyroid adenoma. Biopsy of the bones showed what is considered typical of Paget's disease—excessive osteoid reaction, marked osteoclasis and

hyperplasia of osteoblastic tissue. The immediate result after operation was great general improvement. The femur looks less swollen, and the patient is able to walk without pain. This report is given after two months' observation only and with some reservation. Even after this short time the X-ray shows some improvement. The fuzziness of the thickened femur has decreased, by actual measurement of the X-ray, two to three millimetres, and some normal trabeculation is returning in place of the osteogenetic tissue. (Fig. 5.)

CASE III.—V. J. T., fifty-three years old, a priest, had a typical Paget's disease for ten to fifteen years. His hat size changed from seven and one-quarter to eight and one-half and he grew five inches shorter in ten years. During the same time he became more deaf. He had become very weak in muscular strength in the last two years and had great pain in his hips. Typical Paget's disease was shown in the X-ray with a calcium reading of around eleven milligrams. After many consultations at different clinics a parathyroidectomy was performed on November 11, 1931. Two hyperplastic

FIG. 8.

FIG. 9.

FIG. 8.—Mrs. S. F., fifty-five years old. Arthritic type. Kyphosis, backache, demineralization of spine, hyperostosis and calcified mesenteric glands. Calcium twelve milligrams, chronaxie .41/1000. Note arthritic and hyperostotic processes in the kyphotic spine. Marked clinical improvement after operation.

FIG. 9.—E. B., six years old. Juvenile type. Pathological fractures at two and three years (femurs), again at five years. Bluish sclera, enamel defects, bowing of tibiæ, widespread demineralization. Calcium twelve milligrams. Diagnosis fragilitas ossium, but all the earmarks of parathyroidism in all bones.

parathyroids were removed, microscopically, aside from extremely rich vascularization, not showing any outstanding pathology. Exactly six months after this date we had the first opportunity to examine this patient again. He hears 50 per cent. better, as he expresses it. He can walk three miles, whereas before the operation one hundred yards exhausted him. He has straightened up so that he has regained two inches of his lost height. This man is rather a pessimist, therefore his statements are of value. The head size by measurement is the same, sixty-six centimetres. He hears ordinary conversation very well, whereas before the operation we had to shout at him. A watch is heard by holding it close to the ear. The X-ray shows that the peculiar cotton-like (nigger wool) appearance of the outer table of the skull is disappearing and the normal structure of the skull returning. (Figs. 6 and 7.) His blood calcium is 8.6 milligrams per 100 cubic centimetres of serum.

Our advice, although guarded and reserved, would be to do a parathyroidectomy in a case of Paget's disease if recognized long before malignancy supervenes, especially if the case is accompanied by pain in the bones and hypotonia of muscles—symptoms similar to parathyroidism with osteitis fibrosa cystica, and if the X-ray suggests mixed findings of osteitis fibrosa cystica and osteitis deformans. These indications should not be disregarded in the absence of a marked elevation of serum calcium.

(3) *Arthritic Type.*—In our considerations so far, and in the statistics from the literature, the Oppel type of ankylosing polyarthritis for which parathyroidectomy is recommended, and on which, up to 1928, Oppel had reported seventy operations, has not received the attention that it should receive. It is not mentioned in the recent statistics (Helström). Our orthopædic colleagues at Harper Hospital are convinced that parathyroidectomy has benefited some of their ankylosing polyarthritic cases, and they refer these patients quite liberally for consultation as to the advisability of parathyroidectomy and for operation.

This group is characterized by slight elevation of serum calcium, arthritic processes, spur formation around the vertebræ and other joints, kyphosis, moderate decalcification, some compression of vertebræ and lime metastases in anterior and lateral vertebral ligaments, abdominal lymph-glands, costal cartilages, and many internal organs (kidneys, liver, spleen, gastric mucosa, blood-vessels, *etc.*) and muscular hypotonia. Of this group we have had personal experience of thirteen cases with good results in six, two cases with no results, and two with partial results. In three cases the observation period has been too short to register reports. Proper selection of these cases will bring better results.

Besides the reports from Oppel's Clinic, Leriche, in his work on "The actual basis of parathyroidectomy in certain cases of ankylosing polyarthritis," Heineman and Gruda in their "Observations concerning the question of ankylosing spondylitis, and also on the histological changes in the epithelial bodies and thyroid in ankylosing polyarthritis," Jung, of France, and Beresin, of Russia, have given favorable reports on Oppel's work.

Fig. 8 with its legend gives an example of our experience with this type.

(4) *Juvenile Type.*—We have operated upon three children and three adults where the disease started in infancy and was first regarded as osteochondroma, fragilitas ossium or osteogenesis imperfecta. We have found in this group that a good many had changes in the skeleton generally, especially in the skull, suggesting osteitis fibrosa cystica by its fine granular mottling; muscular hypotonia with frequent falls and serum calcium of at least the higher limits, and we have the impression that some of this group were caused by early or congenital parathyroidism. Our experience is not great enough for us to make positive statements, but striking enough to draw attention to the possibilities.

Shallow, of Philadelphia, has also published such a case and called it an arrested type of parathyroidism, arrested because the process seemingly stopped after one leg had become much shorter than the other on account of the osteitis fibrosa cystica affecting the epiphyseal lines and on account of the rest of the skeleton seemingly not being affected. But we think this type also stays more or less progressive and persevering in its symptoms. Even in the type with blue scleræ and osteochondritic changes usually considered forms of arrested embryological development, and therefore excluded from the endocrine types, it cannot be clearly stated whether or not fetal

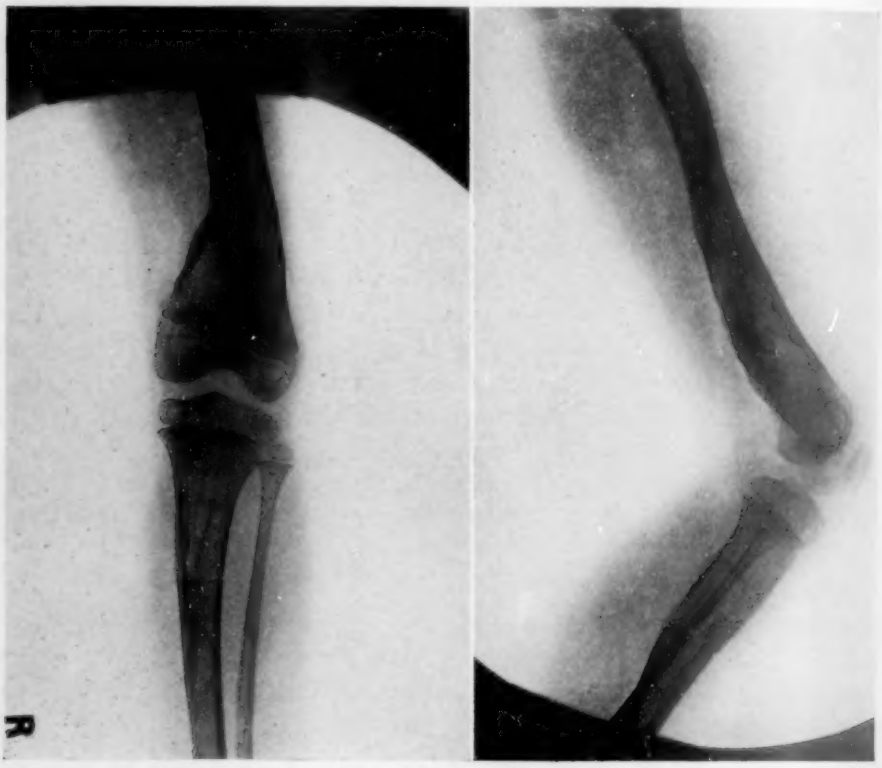


FIG. 10.—E. N., ten years old. Pathological fracture of left femur in 1926, extensive destruction of cancellous bone, two more fractures since, now left leg two inches shorter. In whole skeleton mild changes of osteitis fibrosa cystica (arrested type, Shallow), our own observation, improving after parathyroidectomy.

or early in life acquired parathyroidism is responsible. (Figs. 9 and 10.) For instance:

CASE IV.—Miss J. R. G., now thirty-five years old, was always small—dwarfed since childhood, with very fine intellectual development, had attacks of pain in the long bones, frequent falls, X-ray changes in the spine, decalcifications in the long bones, mushroom forms of femur heads. But now after thirty years she shows X-ray signs of osteitis fibrosa cystica, high calcium and low phosphorus readings, severe muscular hypotonia with frequent falls, and off and on she injures her bones—no doubt a clinical picture of parathyroidism.

All these types of juvenile bone disturbances should be re-studied, especially the fragilitas ossium and achondroplasia, *etc.* A few of our figures will illustrate our own experiences.

(5) The *Myasthenic type* of parathyroidism deserves prominent attention. Hypotonia of the muscles is often such an outstanding symptom that some patients are grouped as myasthenia gravis, muscular atrophy, or spinal-cord tumors, *etc.* The skeletal symptoms may not be as prominent in this type as the hypotonia. For instance:

Case V.—Miss M. F., nurse, aged forty-five years. Except in her twenty-fifth year when she had pulmonary tuberculosis which was absolutely arrested by sanitorium treatment, this patient enjoyed good health, worked every day and was very lively in her movements and actions. In 1926, she had her first attack of pain in the scapula and arms, which improved within a few weeks. She was diagnosed as "myositis" at that time. In November, 1931, she complained of backache which became so severe that she had to give up her nursing. She became weak, her lively gait became very much slower and she found it necessary to ride even short distances to get around. "Back and leg ache" was prominent, also the arm and hand movements became painful. The X-ray showed only a small area of cystic condition in the ilium just below the right sacro-iliac joint. There was some hypertrophic arthritis, not extensive however, around the vertebræ and the sacro-iliac joints. The usual orthopædic treatment, medical and dental care, *etc.*, gave no relief. The serum calcium during the observation ran from ten to thirteen milligrams. The serum phosphorus ranged from two and one-half to three milligrams. The chronaxie was lengthened to 0.3/1000 which is quite characteristic of hypotonia. The symptoms progressed so that she was confined to bed. The R-T interval was reported "just below normal and suggestive of hyperparathyroidism." Rest in bed gave no relief. The hypotonia, the clinical symptoms of muscular weakness, the chronaxie and electrocardiogram suggesting parathyroidism, parathyroidectomy was agreed upon and performed January 7, 1932. The specimen showed hyperplasia of the parathyroid body with new acinar tissue undergoing cystic change. The pain in the muscles and limbs for which morphine was required ceased immediately. Within six weeks she was herself again and returned to her work. The pain has not entirely disappeared, but is of a superficial type brought on by hand shaking, *etc.*, as is seen in many cases of parathyroidism. This patient was operated on rather early on account of the hypotonia, before severe bone changes were present. The results warrant the early operation.

Case VI.—J. A. B., a woman, fifty-four years old, in charge of a large industrial first-aid station. At the age of thirty-three years she had early menopause brought about by surgery for pelvic inflammatory disease. She became very fleshy and in 1930 weighed 200 pounds. In spite of this fat she said that her muscles were so weak that "they quivered" (a symptom also mentioned by Rowntree). She fell several times without any stumbling—the legs "just gave away." There were also some gastro-intestinal symptoms without any clinical findings in the X-ray, *etc.* The basal metabolic rate was plus twenty-five without appreciable goitre. Serum calcium went from eleven to thirteen milligrams. The urinary calcium output was twenty-three milligrams for twenty-four hours. X-ray of the skull showed some erosion of both inner and outer tables, especially in the occipital region, and some hyperostosis in the frontal region. Calcification of the pineal gland. This process in the skull was not diagnostically characteristic to our röntgenologist. There was a striking calcification of the nucleus pulposus between the first and second lumbar segments and calcium deposits over the anterior aspect of the lower dorsal segments. (Fig. 11.) From the hypotonia, frequent falling and X-ray changes, especially the metastatic calcium process, we made the diag-

nosis of arthritic type of parathyroidism with outstanding hypotonia. We did a parathyroidectomy September 19, 1931. The parathyroid tissue removed showed cystic changes. Two lower parathyroids were removed with a subtotal thyroidectomy. The result is striking as far as the hypotonia is concerned. She is back at her work and has not been subject to frequent falls as before the operation. She is still treated with calcium, but her blood calcium has returned to normal—8.8 to 9.2 milligrams since her operation.

Such cases have also been published by Frank and Allen and commented upon by L. C. Rowntree, by Compere, Hunter, *et al.* Frequent falls without good reason and muscular weakness should suggest the possibility of parathyroidism.

FIG. 11.—Miss J. A. B., fifty-four years old, 200 pounds in weight but extreme weakness of muscles, falls frequently, a few fractures, severe backache. Note calcification in intervertebral disc marked. Calcium twelve milligrams. Parathyroidectomy. No falls since, no pain or muscle weakness (eight months' observation).

We have made a good deal of progress in diagnosing this type of parathyroidism in that we have several methods of measuring the hypotonia of muscles accurately. Oppel mentioned, and uses frequently, the simple DuBois Reymond test, and states that it takes four milliampères of current to cause contraction in the normal muscle, whereas it takes seven milliam-

pères in a parathyroidism muscle. The muscle in tetany contracts with two milliampères. This test seems to be fairly constant and is used a good deal in Europe as a symptom in tetany and parathyroidism.

Lapique originally introduced the conception of chronaxie as an electric time coefficient of neuromuscular excitability defined as a minimal time in which current must pass through a muscle or nerve in order to elicit a reaction. Fredericque and Bourguignon, from France, and David Wechsler, in this country, have written on this subject. To be brief, it takes normally 0.24/1000 of a second (0.00024 or 24 sigma) to get a reaction from the flexor pollicis; in tetany it takes only from 0.12/1000 to 0.14/1000 (0.00012 to 0.00014 of a second or 12 to 14 sigma); and in parathyroidism the time is lengthened to 0.48/1000 of a second. Bourguignon in his article claims that the lengthening of the chronaxie in parathyroidism is more reliable than

Parathyroidism

Serum calcium & Chronaxie

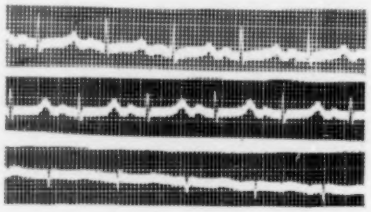
Age	Parathyroidism Type	Serum calcium Pre Op.	Serum calcium Post Op.	Chronaxie Pre Op.	Chronaxie Post Op.	
61	Vertebral o.f.c.	11.6		0.19		*
44	Pain & Hypotonia	10.5	11.0	0.30	0.27	
40	Vert. o.f.c. "	10.4	10.45	0.24	0.24	
75	" "	12.9	9.48	0.33	0.16	
74	Vert. & Hypotonia	9.5		0.32		
55	Vertebral	13.7		0.41		
48	"	12.0		0.40		
45	"	10.9		0.30		
62	Paget monostotic	12.7	10.97	0.36	0.23	
63	Vert. & Hypotonia	10.0	11.4	0.16	0.16	*
10	Path. fractures o.f.c.	10.0		0.32		
50	Skull changes	13.3	9.48	0. 35	0.16	
26	Tetany	10.0		0.14		
26	"	6.-7		0.14		

FIG. 12.—Chronaxie tabulation.

the serum calcium, and that it returns to normal after parathyroidectomy more quickly than do the serum calcium and phosphorus. Generally this agrees with the observations Dr. Plinn Morse has made on our patients. A few exceptions, however, have occurred which may be errors in technic, or most likely due to some other reason interfering with this test. The method, however, deserves attention, and has become a great help in our diagnostic facilities for parathyroidism. (Fig. 12.)

Dr. E. D. Spalding, of Harper Hospital, has observed that the electrocardiogram will show changes in the excitability of the heart muscle similar to the changes in voluntary muscle. In tetany there is a delayed relaxation of the heart muscle, therefore the R-T interval, which normally lies between 0.26–0.28 second, is delayed to 0.30 to 0.34 and even as high as 0.39 second. After implanting some parathyroids in a case of tetany following thyroidectomy, this R-T interval returned to normal of 0.26–0.28 second. In parathyroidism the opposite happens. In one outstanding case the R-T interval

went down to 0.22 second and rose again after parathyroidectomy to 0.27 second. (Figs. 13 to 16.) This electrocardiogram will perhaps become more



EKG on which original observation was made September 14, 1927.
Case M. McD.—Thyroidectomy with postoperative tetany.
R-T = .34" (Normal R-T = .26" to .28")

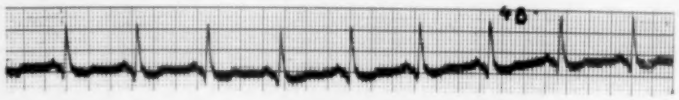
FIG. 13.—Electrocardiogram in tetany.

of a clinical method for measuring the muscular hypotonia than the somewhat difficult chronaximeter. (However, our chronaximeter built by Dr. Plinn F. Morse allows the test to be very easily taken.)

Case M. D.—After parathyroid transplant.
R-T = .24"

FIG. 14.—Electrocardiogram in tetany.

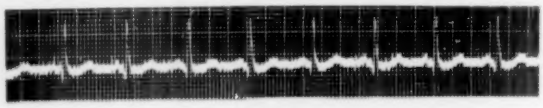
Doctor Rowntree has taken motion pictures of patients to illustrate the clinical manifestations of muscle weakness and also the vascular pulsations at times noticeable on account of the muscular weakness. He showed in



Case H. B.—Hyperparathyroidism with extensive bone changes.
R-T = .22"

FIG. 15.—Electrocardiogram in parathyroidism.

motion-pictures a patient, supine on the floor, who in attempting to rise had to roll over and climb up his legs in the manner of patients with pseudo-hypertrophic dystrophy.



Case H. B.—After parathyroidectomy.
R-T = .26"
(Dr. E. D. Spalding.)

FIG. 16.—Electrocardiogram in the same case after parathyroidectomy.

We also have taken some motion-pictures, and the one I will present shows first, an interne walking with a normal gait; second an outspoken case of parathyroidism who can hardly walk the short distance from one chair to another, ten feet distant, slowly dragging her legs, and bent over; and third, the same patient four weeks after removal of a parathyroid tumor walking at a much livelier gait and with much better carriage.

Therefore, we have five means of determining the muscular hypotonia. First, the clinical symptoms of slow gait and frequent falls; second, the simple method of measuring by milliampères the current needed to cause muscular contraction; third, the much finer and more dependable chronaxie

FIG. 17.

FIG. 18.

FIG. 17.—Mrs. C. L., forty-five years old. Typical scleroderma, sclerodactylia, *etc.* Calcium eleven milligrams. Phosphorus 2.2 milligrams. Note immobility of the wrinkled skin of the lips.
FIG. 18.—Same patient as Fig. 17 within two weeks after parathyroidectomy. Marked difference in appearance of lips.

determination; fourth, the R-T interval in the electrocardiogram; and fifth, the motion-pictures of the patients.

Besides the two cases mentioned, we have had in our experience many others who have had marked hypotonia of muscles along with other symptoms.

The five groups are not entirely separable from each other as already suggested by all symptoms being more or less present in each one, but characterized by one symptom being outstanding.

One of the rarer symptoms of parathyroidism for which parathyroidec-

tomy has been recommended is scleroderma. Leriche has reported six parathyroidectomies and ligatures of the parathyroid artery for treatment of this condition apparently with success. I operated upon an outspoken case of scleroderma two months ago. The results so far seem to confirm Leriche's observations, but I reserve a final report of this condition for a later date. (Figs. 17 and 18.)

Treatment.—The general impression prevails that medical treatment—the administration of calcium salts, the support of absorption by giving vitamins in irradiated cod-liver oils, ultra-violet rays, *etc.*, should be tried. Some forms are initial and perhaps transitory. In our own experience we have had patients after faulty diet or having acquired osteomalacic conditions in puerperium, seemingly affected with parathyroidism, who have improved at least temporarily under such care. But an outspoken case with cardinal symptoms more or less present (not all are necessary) or with recurrence of symptoms after a temporary remission, should be operated upon.

Experience has now brought out very forcibly that it is not always large adenomatous tumefactions of the parathyroids that cause the disturbance. A parathyroid of normal size, without any recognizable gross change, can cause hyperfunction. Richardson, Vaughan, and we have had cases where the removal of seemingly normal parathyroids stopped severe processes of osteitis fibrosa cystica. Our co-worker, Dr. Plinn F. Morse, writes:

> There seem to be two general types of hypertrophy, the compact type in which the cells merely proliferate in the form of a compact, uniform mass within the capsule, the whole gland appearing as a dense and uniform structure composed of chief cells with occasional acidophilic elements scattered through it, the whole being inclosed in a uniform fibrous capsule. This type of hypertrophy is particularly common in younger individuals and in individuals in whom the parathyroid apparently has hypertrophied compensatorily in response to a physiological need, such as osteomalacia, rickets and renal rickets. On the other hand, in the cases which we prefer to call primary parathyroidism at this time, which occur in older individuals and express themselves clinically as osteitis fibrosa cystica or Paget's disease, we find a type of hypertrophy consisting apparently of increase in peripheral lobules, so that the gland spreads out and becomes more diffuse with new forming lobular collections of cells at the periphery, with considerable amount of fat tissue between them. This loosely arranged structure of the parathyroid, in the normal individual, is more characteristic as age goes on and the senile gland in general is much more loosely arranged with a great deal more fat between the lobules than is the case in the glands of younger individuals.
>
> The analysis of the cases so far published as well as a perusal of the microscopical findings in our own cases will make it evident that the question of parathyroidism is not one of microscopical structure of the gland. In the early part of this work all operators expected to find a parathyroid tumor. It became immediately evident that the tumor, in the sense of a neoplastic growth of the parathyroid, was practically never present. Various degrees of enlargement of adenomatous character, sometimes quite marked, were common findings in the outstanding forms of osteitis fibrosa; but many cases with outstanding bone changes and disturbances of calcium metabolism showed no gross enlargement, or at least very doubtful gross enlargement of the gland. However, the brilliant clinical results obtained by removal of one or more of these bodies seem to justify that the dyscrasia is a functional one, having to do with functional over-

activity or possibly a glandular inbalance which is corrected by removal of some of the parathyroid tissue, and as a final consideration it must be borne in mind that there is no strict parallelism between the microscopical findings in the parathyroid and the clinical results which follow removal in cases in which the characteristic clinical, röntgenological and chemical findings make a diagnosis of parathyroidism justified.

Up to now fatal tetany has been reported four times, in three cases immediately after operation (Beck, Wanke, Ask-Upmark), and the fourth a more chronic type (Eggers) seven months after operation. This case was reported as suffocation from a fibroma of the vocal cord found at autopsy, but had all the ear-marks of tetany. In all four cases the surgeon looked

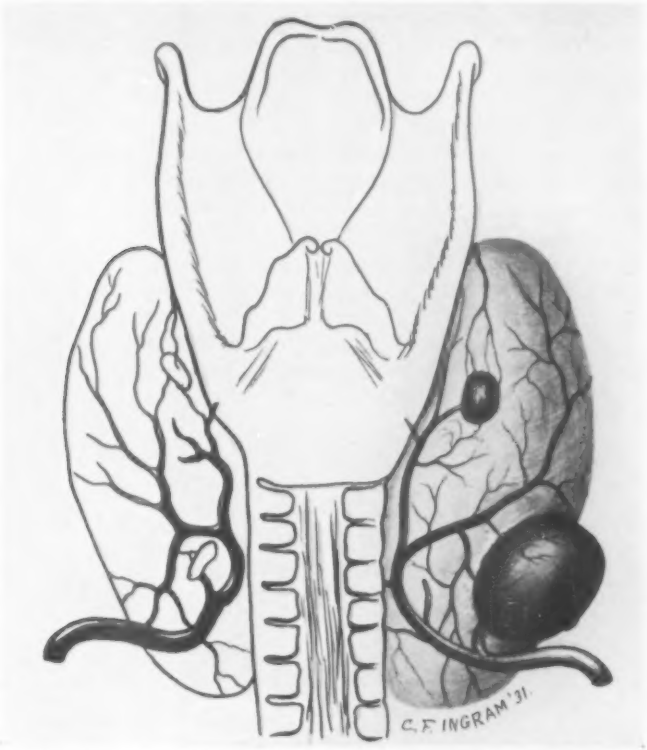


FIG. 19.—Mrs. H. C., sixty-three years old. Large parathyroid adenoma in well-marked classical vertebral type of parathyroidism shows the importance of surveying both parathyroid regions first, before starting to remove parathyroids. If the two on the left side were uncovered and removed first, the large tumor would have to be removed also and tetany would probably be the sequela.

first on one side and took out what he found—one or two parathyroids; then looking on the other side, he found a large adenomatous gland, so that three parathyroid bodies were removed. For this reason, we strictly advise, before removing any parathyroid tissue, a survey of both parathyroidal regions. (Fig. 19.) By means of a towel clip, first the left, then the right thyroid lobe (or vice versa) can be turned over mesially, and we can see at least if there is any gross tumefaction of the parathyroids present on either side before we start the parathyroidectomies. In one of Helström's cases, one

large adenoma was removed from one side. The patient improved only temporarily. The calcium stayed high. The symptoms returned in a few weeks and a second parathyroid adenoma was found on the other side at a second operation. It seems to be safer to do the operation in cases of several large parathyroids in two sittings than in one, so that gradual accommodation takes place instead of sudden tetany. Compare the two-stage lobectomy in cases of severe thyroidism. Routine biopsy by frozen section of all material removed will protect the surgeon from disappointment such as we had early in our work a few times, getting a report later than the tissue removed did not contain parathyroid elements. In all our parathyroidectomies postoperative administration of parathormone and intravenous calcium is given until the serum calcium level is constantly normal, generally for about one week, so that even suggestive symptoms of tetany have been entirely avoided.

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Sainton, Hotel Dieu, Service d'electro-radiotherapie de la salpetiere et service de medicine. (See Bourguignon and Sainton.)

DOCTOR PHEMISTER (Chicago) thought Doctor Ballin's studies to be a real contribution to the subject of obscure skeletal lesions. On the other hand one must be guarded about trying to explain all of them on the basis of parathyroid disease. In the past four years he had determined the calcium and phosphorus content of the blood in seven cases of solitary bone cyst, three cases of regional osteitis fibrosa and ten cases of Paget's disease. In none of them had there been elevated blood calcium or lowered blood phosphorus. The solitary bone cysts are all easily cured by local operation, which speaks strongly against their being of parathyroid origin.

DOCTOR BALLIN rejoined that bone cysts are a subject of great controversy. They may not all belong to the entity, parathyroidism, but the results of parathyroidectomy on these cysts at least give some suggestion that many of them are of parathyroid origin. For instance, Barr and Bulger, also Donald Hunter, have published several cases of multiple cysts in the jaws. Some of them were scraped out and healed, but some returned. After parathyroidectomy all the cysts healed, without being touched.

About the high calcium: he had gone through a similar period in his thyroid experiences. For some time he hardly ever operated on goitres unless they had high basal metabolic rates; the same here, if most of the clinical symptoms of parathyroidism are present, high calcium is not always necessary; in fact, the French have published an article lately where they look much more to the hypotonia of the muscles for guidance than to the calcium finding. Muscle hypotonia may be measured by chronaxie and by electrocardiogram. Chronaxies are the mathematical expression of the time factor intervening between the least stimulus and the contraction of a certain muscle. The normal chronaxie for the flexor digiti quinti is .28/1000 of a second. In parathyroidism this figure goes up to .40/1000 and .50/1000 of a second; in tetany, on the other hand, it goes down to .18/1000 of a second. (Dr. Plinn F. Morse.)

This muscle weakness also shows itself in the electrocardiogram. The R-T interval is shortened in parathyroidism and lengthened in tetany. (Dr. Edward D. Spalding.)

He had many observations now showing these two tests to be reliable. If he operated on cases of parathyroidism only if they have fifteen and twenty and more milligrams of calcium per 100 cubic centimetres of serum, he was sure they would miss a good many cases that could be helped. The serum calcium is not high all the time; there are intermissions and other factors disturbing this test.

ANEURISM OF THE INNOMINATE ARTERY

By Arnold Schwyzer, M.D.
of St. Paul, Minn.

In regard to the treatment of aneurism of the innominate artery considerable pessimism is encountered in the literature. Up to 1902, Jacobsthal had found among 120 cases of combined aortic and innominate aneurisms reported by him as treated by distal ligation, only two living more than three years after operation. Last year, LaRoque, in a paper in the April number of the Annals of Surgery, declared: "Aneurism of the innominate artery has never been removed. The vessel has been ligated several times, and in the few that survived the operation, some benefit but no cure has been attributed to it." This statement is, however, not quite correct. Imai, a Japanese, published a case of excision of a small hen's-egg-sized aneurism, which at the time of writing, four and a half years after the operation, was in good condition. (Deutsche med. Wochenschr., 1913.) Rosenstein, of San Francisco (Osler, Modern Med., 1927), operated upon a perforating case. The patient is said to have lived many years after. Da Costa made a distal ligation of carotid and subclavian arteries in two cases, one of which appeared cured five years later, after which he was lost track of. Guinard, of the Hotel-Dieu Hospital of Paris, wrote in a rather optimistic spirit on the subject of distal ligation in the Revue de Chirurgie, February 10, 1909.

Without going further into the literature of the subject, I will simply report a case which to my knowledge represents an unusually long observed operative result. F. J. R., of Havre, Montana, came under my care on November 7, 1909. His history was in short the following: He had acquired lues in the spring of 1903. The medical treatment was very short and entirely inadequate. He felt, however, well until in April, 1909, he noticed a small pulsating bulb above the right clavicle. Gradually this pulsation became more marked. With the appearance of the protrusion (Fig. 1) some pain came on in the right shoulder and on the inner side of the right arm. He did not see a physician until June 1. By that time the pulsation was strong. He was immediately put to bed, and after a few days sent on a stretcher to St. Paul. Here he was kept flat on his back under the charge of a prominent internist. A surgeon was consulted, and he advised against operative interference on account of the threatening appearance of the pulsating mass. Mercury inunctions, K.I. and calcium lactate were given. When seen on November 7, patient had been flat on his back for over five months, and during the last six weeks had not been allowed to raise his head even while eating.

The examination of the otherwise healthy man of thirty-one years showed a strongly pulsating tumor on the right side of the neck, reaching from the mid-line in the jugular fossa to the posterior edge of the scaleni region. With its upper conical, though rounded outline, it reached to a level with the upper portion of the thyroid cartilage. The lower edge of the bulging extended down over the anterior surface of the clavicle. The transverse diameter of the mass from the jugular fossa toward the right and back measured six and one-half centimetres. The point of greatest bulging was one and one-half centimetres above the clavicle just laterally to its head. In the jugulum extensive pulsation was felt as far as the finger could enter on deep pressure. Pulsation in the carotid cephalad from the aneurism seemed to be weaker than on the left side. In the

first and second interspace below the right clavicle there was some dullness, but no pulsation was made out. This finding is of interest because a radiogram which the patient sent me two months ago (March, 1932) shows a normal condition of the aorta. This radiogram makes it definite *a posteriori* that we were dealing with an aneurism which was localized to the innominate artery, and not involving the aorta. All the heart sounds were normal. Both radial pulses were synchronous, while as to the temporal arteries we were in doubt. They were then examined in the following way: After both pulses are first well established under the fingers, then the examiner, seated behind the patient, closes his eyes and remains in the same position for some time until he is not conscious of the position of the hands. He can now imagine that he feels the same blood vessel at different levels. While before it had been uncertain which side was beating first, it now appears plain that the blood in the supposedly single vessel runs from under the left hand to the right one; in other words: the pulse in the right temporal was a little retarded. Digital compression of the carotid was then done repeatedly up to three minutes at a time, in order to give us assurance

FIG. 1.—Aneurism of the innominate artery, November, 1909. Anterior and lateral views.

that ligation would not cause dangerous cerebral symptoms. The pulse ranged between 72 and 96; the temperature was normal.

November 23, 1909, the operation took place at St. Joseph's Hospital. Before the ether narcosis was started, both legs were tied off near the groin in order to sequestrate a large amount of blood by passive hyperæmia. Thus we thought to reduce the blood-pressure and secure a reserve supply of blood for an emergency. An incision was made in the skin-fold over the sternomastoid muscle near the upper border of the mass. The common carotid was freed directly behind the upper pole of the aneurism and ligated with No. 3 formalized catgut after we had assured ourselves that the arterial walls felt normal. The skin was closed and a second incision was now made above the outer portion of the clavicle and parallel to it. The brachial plexus had to be pushed outward and backward and the aneurismatic sac inward, after which the third portion of the subclavian artery was reached. Guinard's statement that these aneurismatic sacs after freeing can often be dislodged and compressed quite freely proved to be very correct in our case. After ascertaining again that the artery was normal in size and flexibility, it was ligated with No. 3 formalized catgut and the skin closed. The pulsation in the aneurism had not changed by the time the dressing was put on. Pulse and respiration had remained unaffected during the operation. Tonometer readings* had been made on each arm previous to the operation before and after sequestrating

*Tonometer readings were done in those days by taking the lowest pressure at which the radial pulse disappeared.

the blood into the legs. The sequestration had made no difference in the readings. On the right arm the systolic pressure had been 100 millimetres mercury, and on the left 112. After the operation the blood-pressure in the left arm was 110; on the right wrist no pulsation could be felt. The pulse rate at the end of the operation was 90. The right arm was wrapped in cotton. For four hours the arm remained cold, but after that it warmed up. Eleven hours after the operation the hand was quite warm and there was no trace of pain in the arm. Good motion and sensation. On the following morning there was some faint pulsation at the right wrist. Forty-eight hours after the operation the patient was allowed out of bed. On the following day the dressings were changed for inspection . Even on close examination there was now only a vague impulse to be seen apparently transmitted by the rigid thrombosed sac. On the tenth post-operative day our patient left the hospital.

Three years later he married. In December, 1914, he had a bad runaway and was dragged for some distance. His right wrist was broken, and he received many bruises, but the aneurism did not seem to make any trouble. Upon my inquiry he wrote in

FIG. 2.—Photograph taken in October, 1931, twenty-two years after operation.

October, 1931, that he felt splendidly (Fig. 2); that he had continued general ranch work, including the breaking of bronchos, until 1923—in other words, for nearly fourteen years after the operation. He further stated: "It was financial trouble and not physical disability that made me quit the ranch life."

In regard to the operative procedure it is much the best to ligate both arteries at the same session. The walls of the arteries should not be calcified nor even markedly atheromatous at the place of ligation, as otherwise it may occur that a secondary aneurism develops at the site of ligation, like, for instance, in Da Costa's second case. Guinard emphasized as of greatest importance that the carotid be taken care of first, because otherwise, as it happened to Riche (Guinard, *l.c.*), due to the suddenly changed whirls in the aneurismatic sac, loosely attached parietal thrombi might be thrown into the cerebral vessels. Due to the free communication between the right and

left external carotids a reversed flow of blood occurs in the external carotid of the ligated side which then supplies the corresponding internal carotid. This renders ligation of the common carotid much safer than that of the internal. Terrier observed while ligating the common carotid that the temporal artery kept right on pulsating as before. It is claimed that ligation of the common carotid causes intracranial complications in from 20 to 25 per cent. of the cases and that half of these die. The Swiss ophthalmologist Siegrist, gathered 997 cases of ligature of the common carotid (v. Graefe's Archiv fuer Ophthalmologie, 1900) and came to the conclusion that the danger of ligating one of the common carotids is really very slight if severe atheromatous changes and wound infection with consequent ascending thrombosis or secondary hæmorrhage are excluded. The remaining deaths were mostly *not* due to the ligation itself, but to pre-existing causes like a serious heart lesion or a greatly debilitated condition in malignant disease or after severe pre-operative hæmorrhage. However, some of the deaths were due to faulty operating causing injury of the vagus nerve. Impressed by this study, Guinard made an examination of the fatalities of ligature of the common carotid in his own cases and those of the other members of the Paris surgical society, and showed them due either to obliteration of the carotid of the other side or to a serious damage to the intercommunication between the two external carotids, as after operation for malignancy of the maxillary area. Excepting these two contingencies he declared flatly that the mortality in ligation of the common carotid is "absolument nulle."*

Babcock emphasizes the increase of the intra-aneurismal pressure when distal ligation is made. At the moment of ligation this is of course true, but physiological study of the function of the cardiac depressor nerve indicates that the blood-pressure in the aorta is well adjusted to the requirements of the blood supply to the vital organs. Furthermore, our case shows that the sac was very soon thrombosed enough to transmit only a vague impulse and that expansion had ceased. It might be of help to use some kind of support or compression for that length of time in case perforation is imminent. Babcock's procedure of carotido-jugular anastomosis appears to be very valuable for aneurisms of the thoracic aorta; but when performed for aneurism of the innominate artery, it renounces from the start the attempt to obliterate and thus completely cure the aneurism.

The result in our case has now lasted twenty-two and one-half years, and it would be hard to pick out severer tests after operation for a large innominate aneurism than run-aways and broncho-busting. However, we were favored by two factors of importance, first and before all the limitation of the aneurism to the truncus anonymus leaving the aorta uninvolved, and second the healthy condition of the arteries at the site of ligation.

* I have ligated the common carotid several times without untoward symptoms. In two cases it was for aneurism of the internal carotid. One of these was an aneurism in the cavernous sinus with exophthalmus pulsans. The patient, a woman, was reported to be well eleven years later. The other, also a woman, had her aneurism directly above the sella turcica. She was operated upon four years ago and is well today (published in Minnesota Medicine, August, 1930).

SUBCLAVIAN ANEURISM

By Ellsworth Eliot, Jr., M.D.
of New York, N. Y.

The subject of subclavian aneurism is most conveniently divided, as is aneurism in general, into those of the spontaneous and those of the traumatic varieties.

From a long period, extending over several centuries, the clinical features and the pathology of the spontaneous variety and to a certain extent its surgical treatment as well, have been thoroughly standardized. On the other hand, in aneurism following penetrating wounds or other forms of trauma, the symptoms and treatment are still in such a formative stage that further study and discussion are required.

The treatment of spontaneous subclavian aneurism was presented by the writer in a paper read before this Association in 1912. Proximal ligation was then, and still is the operation of choice which, if unsuccessful, may subsequently be supplemented by distal ligation with or without excision of the sac. In aneurisms of the first portion of the vessel, ligation of the innominate must be done. In aneurisms of the second or third portion the ligation of the first part of the artery may be supplemented by ligation of the internal mammary and thyroid axis. If the artery proximal to the aneurism is atheromatous, distal ligation as close as possible to the aneurismal sac is justifiable. Pearson, in a case of this kind, permanently cured an aneurism of considerable size by distal ligation after an attempt to ligate the first part of the artery disclosed an extensively sclerotic condition in which the artery was adherent to its sheath, and to the cervical plexus.

The exposure of the innominate or of the first part of the subclavian is facilitated by the resection of the inner end of the clavicle with or without the adjacent part of the manubrium of the sternum. In the ligation of the deeper part of the left subclavian a satisfactory exposure of the vessel can be secured through the posterior medistinum.

All kinds of absorbable and non-absorbable material including chromic gut, silk, kangaroo tendon, linen bands, fascial strips, together with special clamps such as those devised by Halsted, have been used in different varieties of ligation with equal success. Successful ligation of the abdominal aorta is still relatively an unsolved problem. The form of knot has also varied, the double ligature being favored. The patient of Hamann, who used braided silk, and of Vaughn, who used tape, survived the operation and lived for six months and two years respectively. At present fascial strips, especially in the ligature of large vessels are generally preferred. Campbell, who has used this material in the ligation of the common carotid in three instances and of the popliteal in one, states that "simple ligation and treat-

ment by other methods has not given nearly such good results in my hands or in the hands of my colleagues."

The paper above referred to gave the clinical history of a patient suffering from a spontaneous aneurism of the third part of the right subclavian artery, in which a cure was effected by a ligation of the first part of that vessel. The ligation of the main artery was supplemented by separate ligation of all its branches with the exception of the vertebral, in order that a clot of sufficient length and strength might diminish the possibility of secondary hæmorrhage when the lumen of the vessel was opened by the cutting through of the ligature. At the end of five years no recurrence had developed and during the last four years of that period no precaution had been taken in restricting the use of the right arm. A Wassermann reaction, however, still gave a four plus positive reaction. At the end of twelve years the patient's condition was unchanged.

I am indebted to my former resident, Dr. Ralph Colp, of New York, for permission to add the end-result in the case of a patient presented to the New York Surgical Society, in which a subclavian aneurism on the right side was treated by a similar operation. Doctor Colp informs me that the aneurism had shrunk to the size of a tennis ball and that it was of firm consistency at the end of two years when the patient suddenly died from the effects of an apoplectic seizure.

The ligation of the branches of the subclavian artery in these two cases necessarily eliminates channels through which a considerable part of the collateral circulation would ordinarily be established. The fact that in both patients the radial pulse returned (in the writer's case, on the fourth post-operative day; in Doctor Colp's case, somewhat later) and that no œdema or circulatory disturbance persisted, indicates that the anastomosis between the thoracic intercostals and the thoracic branches of the axillary was sufficient to provide an adequate collateral circulation. Hertzler reports a case in which three weeks after the successful ligation of the innominate for subclavian aneurism the vertebra and common carotid arteries were ligated for a recurrent pulsation without ill effect. Guleke also reports a case in which the ligation of the subclavian was supplemented by the simultaneous ligation of its branches without subsequent circulatory interference.

While this measure does not seem to impair the establishment of adequate collateral circulation, it does not always avert the danger of secondary hæmorrhage. In the case of an identical operation to control the hæmorrhage due to extensive wounds from a shell fragment in the right supraclavicular and axillary regions, which occurred during the Argonne campaign, secondary hæmorrhage developed during the third week following the operation from the penetration of the lumen of the main vessel at the point of ligature from the effects of which and from the intense infection the patient died. The presence of infection markedly predisposes to the occurrence of this unfortunate complication irrespective of the type of operation employed.

whether ligation, the reconstruction of the arterial continuity by suture or the endo-aneurismorraphy of Maras.

Another greatly-to-be-feared sequela of operation for aneurism is gangrene of the extremity. While this may be due in part to lack of an adequate number of anastomotic channels, the presence of infection undoubtedly plays a much more important rôle. In pre-antiseptic days the simplest ligation was necessarily subject to infection. The thrombosis in small blood-vessels divided in the exposure of the main arterial trunk might spread to such an extent as to permanently occlude many vascular channels on the patency of which the establishment of adequate collateral circulation depended. Although in the aseptic operation of today such an unfortunate diffuse thrombosis is avoided, the bug-bear of gangrene, especially in war surgery in which infection is such a common complication, persists.

It is generally agreed that gangrene is more common after operations for traumatic aneurism than after those for the spontaneous variety. In the latter the possibility of post-operative infection can usually be eliminated. Furthermore, because of the interference of the normal flow of blood through the aneurismal sac, the establishment of a partial collateral circulation has usually taken place. While in this group the presence of atheroma, if diffuse, favors the development of gangrene, the general weakness from the loss of blood and the consequent diminished blood supply of the affected extremity are factors of considerable importance in the traumatic variety. Moreover, in this same variety the damage to the main artery is not infrequently associated with simultaneous division and consequent occlusion of many of its collateral branches. In this connection the statistics collected by Wolff are of the greatest interest for they include the consideration of several hundred cases of gangrene both prior and subsequent to the aseptic era. They show that, in the latter period, gangrene occurred in 4.8 per cent. of the cases of ligation of the subclavian artery and even with much greater frequency after the ligation of other large vessels, the popliteal as in pre-antiseptic times, still showing a relatively high percentage. Lexer, referring to these statistics, states that, in his experience, gangrene is even more frequent than the tabulation of Wolff would indicate, although no specific details are given. On the other hand, in Halstead's statistics based upon 142 cases in which all the various types of operation were done under antiseptic precaution, gangrene occurred in three instances, namely, after a ligation, after an excision and after an endo-aneurismorraphy of the popliteal artery. The testimony of Von Haberer is also of great interest, namely, that in seventy-two cases of wounds of arteries observed during the war only in one did gangrene develop. Bier also states that in fourteen ligations for traumatic aneurism during the war, no instance of gangrene or, in fact, of any circulatory disturbance was noticed. This he largely ascribes to the careful conservation of the branches of the damaged vessel.

While cases collected from the records of a single clinic or from the experience of a single observer are obviously more reliable than a general

compilation gathered from the literature, it must be emphasized that even though no gangrene develop, the interference with the blood current resulting from operations for aneurism, especially for the traumatic variety, not infrequently is followed by pain, muscular contractures, paralysis, atrophies and symptoms of impaired circulation. In Halstead's statistics a case of paralysis is cited after a Matas operation for popliteal aneurism. Wolff also states that of thirteen cases examined by Frish only five were free from some one of these sequelæ. After ligature of the subclavian the radial pulse cannot usually be felt for several days. It then becomes palpable, gaining in force for several weeks, although some permanent weakness persists. In this connection Stewart, from two observations of the flow of blood after ligation of the innominate for subclavian aneurism, states that at the end of a month approximately three-fifths of the normal blood current in the radial artery were restored. Von Haberer emphasizes that the restoration of the circulation is more complete after arterial suture than after ligation and usually enables the individual, if a soldier, to resume full military duties.

To eliminate the possibility of gangrene Matas devised the operation of endo-aneurismorraphy and Lexer, with other German surgeons, developed the restoration of arterial continuity by suture, anastomosis or by the filling of the gap between divided arterial ends with a segment of the internal saphenous vein.

While aseptic surgery has not eliminated the danger of secondary hæmorrhage or of gangrene it has at least extended to a great degree the field of successful surgical therapy. To it must be ascribed the comparative freedom from risk involved in the excision of an aneurismal sac after distal and proximal ligation of the afferent and efferent vessel. It has also made possible the brilliant operation of aneurismorraphy advocated and introduced by Matas. While in aneurism of the subclavian, iliacs, or other large arterial trunks some form of ligation is considered preferable by many surgeons, it is the general consensus that the Matas operation is especially applicable to those aneurisms of the extremities in which the establishment of adequate collateral circulation is doubtful. Yet even this ingenious operation is not free from the risk of gangrene. In 1912 the writer called attention to the fact that this complication had occurred in cases that were never reported. The master hand of a Matas cannot easily be duplicated, even by skillful surgeons in whose experience this operation is relatively uncommon.

Aseptic surgery, in combination with intratracheal anæsthesia, has also made possible the operative relief of intra-thoracic aneurisms of the left subclavian and common carotid arteries in which a healthy segment intervenes between its origin from the arch and the site of the aneurism. In this group the aneurism is exposed, after an X-ray examination, through either the anterior or posterior mediastinum. If the subclavian is involved, the more superficial common carotid, if the anterior route is selected, is a valuable guide especially when an overlying aneurism makes the identification of the former vessel difficult.

The consideration of certain clinical features and of the pathology of traumatic aneurism, especially of the subclavian artery, may advantageously precede a discussion of their surgical therapy. The appearance of aneurisms of this type usually promptly follows the trauma. Exceptionally weeks or months may intervene between the receipt of the injury and the development of unquestioned aneurismal symptoms. In the former group surgical therapy may be immediate or delayed. In the latter group radical measures are impossible until the diagnosis of aneurism is established. In the subclavian artery as well as in the traumatic aneurism of other large accessible vessels the gradual appearance of a swelling having expansile pulsation is essential to diagnosis. The presence of a soft blowing murmur with or without a thrill is a reliable symptom only when the detection of expansile pulsation is concealed by the depth of the aneurism beneath overlying structures. Jastram refers to a patient in whose case a marked thrill with a constant murmur, intensified in systole, developed five months after a perforating bullet wound above the right clavicle without a pulsating tumor. The compression of the subclavian trunk on the proximal side obliterated both the thrill and murmur as well as the radial pulse. Exposure of the supposed aneurism revealed normal subclavian vessels. The thrill and murmur, following the operation, disappeared but gradually recurred and in three weeks had reached their former intensity. These unusual physical signs were ascribed to the narrowing of the vessel by scar contraction. Jastrum refers to twelve similar cases observed by other surgeons with no mention of clinical details.

Cotte also reports a case of absence of the radial pulse after a bullet wound above the clavicle for which, four days afterward, in the absence of a tumor, an exploration was undertaken. No aneurism was found. The wound promptly healed. Ten days later an aneurismal swelling appeared with disturbances in the distribution of the seventh and eighth cervical nerves. The writer recalls the discovery of a soft blowing murmur in the course of the physical examination of the chest of a young man over the mid-clavicular region. There had been no history of trauma and the murmur had been discovered in the course of an examination for an insurance policy. It was ascribed to the narrowing of the lumen of the subclavian artery by pleuritic adhesions over the apex of the lung. The diagnosis could not be substantiated by the X-ray which at that time had not been discovered. No aneurism ever developed and the patient is still alive and well.

The persistence of a murmur after the excision of an aneurism has been observed by various surgeons, including Heinlein. One instance of this kind was observed by the writer after the excision of an arteriovenous aneurism of the temporal artery in the parotid region.

The surgical treatment of aneurism, especially of the traumatic variety, presents several interesting problems. Cases in which the collateral circulation is unquestionably adequate are best treated by the excision of the sac, preceded by ligation of the afferent and efferent vessels. Such an operation is always indicated in aneurisms of the scalp and in the distal por-

tions of the extremities. A similar operation may also be done for aneurisms of some of the larger vessels including the subclavian, although it is contra-indicated when uncontrollable hæmorrhage is likely to occur in the course of the excision of the sac.

In the treatment of aneurisms following penetrating wounds conservative and radical measures have their advocates. The subsidence if not the complete disappearance of aneurisms of small size, even of the larger vessels, through rest, diet, and medical therapy has been noted. The spontaneous cure of traumatic aneurism has also been proved in wounds of the brachial, axillary, subclavian and common carotid arteries by various surgeons in operations performed weeks or months subsequent to the trauma for associated injuries of important nerves. Lehman reports a case in which an aneurism of the eight subclavian and innominate (the latter verified by X-ray) was due to the penetration of the fragment of a shell in 1917. No operation was done (possibly on account of the location and extent of the aneurism). Almost three years later marked improvement was noted, being indicated by a diminution in the intensity of the physical signs and by a greatly decreased area of dullness. For the past three years patient has been working as a draughtsman (1924).

Kirchner reports a case of a small aneurism of the left subclavian above the left clavicle due to a bullet wound through the left shoulder. This, after remaining stationary for ten years, suddenly increased in size subsequent to some unusual exertion requiring ligation of the left subclavian with imbrication of the sac.

Spontaneous cure in these aneurisms is favored by a complete division of the artery which permits the retraction of the divided ends. A persistence of the aneurism is more likely to follow a perforation of the arterial trunk.

Reidel emphasizes the value of the treatment of traumatic aneurism by the local pressure of rubber sponges with overlying sand-bags, supplemented by proximal digital pressure of at first fifteen minutes' duration, gradually increased to an hour. Twelve cases were treated in this way including an aneurism of the left subclavian, the size of a fist, which was cured. A cure also was obtained in aneurisms respectively of the left carotid, the external iliac and the superficial femoral. This method of treatment is contra-indicated if rupture is threatened, or if incipient infection develops. Riedel emphasizes the fact that traumatic aneurism in which the wall of the artery is healthy is more frequently benefited by this measure than a spontaneous aneurism in which atheroma of the involved artery is frequently present. He further states that the danger of rupture diminishes as the aneurism decreases in size and that the complication of embolus from the effect of pressure is not great.

Conservative measures are not without their drawbacks. The gradual formation of the aneurismal sac which, according to Von Haberer, is sufficiently advanced by the seventeenth day to permit its excision, becomes usually so incorporated with the adjacent brachial plexus that a separation

of the nerves is difficult. Moreover, the gradually increasing pressure of the aneurismal sac is manifested by severe pain and motor disturbances in the distribution of the plexus. The pain at times is unbearable while the muscular contractures and paralyses, according to Oudard, show a tendency to become permanent, even though an operation is ultimately performed. These unfortunate complications do not occur when the aneurism has been cured or improved by conservative treatment. The rapid and uncontrollable increase in the size of an aneurism leading to rupture constitutes an actual risk. Syring reports a case of subclavian aneurism due to penetration by a bullet and associated with damage to the vein in which death from hæmorrhage took place eleven days after the trauma before any operation could be attempted.

Immediate operation is indicated in traumatic subclavian aneurism when blood is lost. It is also justified when the hæmorrhage is intermittent although the loss of blood in each instance is not sufficient to threaten the life of the patient. All agree in the advisability of early operation whenever there is injury to the brachial plexus. It must be remembered, however, that complete paralysis may follow contusion or compression of a nerve trunk without its division or laceration. This was repeatedly observed during the war, in the main trunks of the brachial plexus, complicating lacerated wounds of the arm. Early operation must also be done when continuous increase in the size of the aneurism points to the probability of the early rupture of the sac. In war surgery the necessary débridement of the wounds resulting from high explosive fragments or other agents known to introduce highly infectious material is possible only after satisfactory hemostasis has been carried out. Even when subsequent infection is uncommon, as in penetrating bullet or stab wounds taking place in civil life, some surgeons prefer operation for the ensuing aneurism in every instance. It is precisely in cases of this character, however, that conservative therapy in the absence of any complication is likely to give satisfactory results.

Operations for the relief of aneurism include the excision of the sac (to which reference has already been made), the various forms of ligation, and operations to restore vascular continuity either by the Matas endo-aneurismorraphy, or, especially in traumatic aneurism, by suture of the lateral tear in the vascular wall, by end-to-end anastomosis after excision of the damaged segment or by implantation of a segment of the internal saphenous vein between the ends of the divided artery when the length of the gap precludes the possibility of anastomosis without undue tension. Excision or ligation in any form is subject to the risk of secondary hæmorrhage or to gangrene. The former is most frequent after ligation of the largest trunks, especially of the innominate and aorta when the cutting through of the ligature finds the lumen of the vessel still patent. A clot of sufficient length and strength, because of the number and size of its branches, may also fail to follow a ligation of the first part of the subclavian. It is for this reason that the writer suggested in 1912 the ligation of these various branches with the exception of the vertebral.

The suture, anastomosis, or plastic repair of divided arteries advocated especially by Lexer and Hotz and to a certain extent by Bier and Zahradnecky were devised to avert the danger of gangrene. For their success a healthy arterial wall and complete absence of infection are unquestionably essential. When hæmorrhage can be controlled by the application of an Esmarch bandage or by preliminary proximal and distal ligation of the torn or perforated vessel, the operation is relatively without risk. In traumatic aneurism of the subclavian artery the danger of uncontrollable hæmorrhage, either in the course of the operation or subsequently from an insidious or unsuspected infection, is an important factor. Unfortunately, the clinical details in Lexer's essay are very meagre. Yet he mentions one death on the table from failure to check the hæmorrhage from the sac of a subclavian aneurism; a second death from an infected thrombus in a ligated subclavian stump, and a third fatality, also in the presence of infection, twenty-four hours after operation from "myocarditis and sepsis." Five successful cases of operation for traumatic aneurism in arteries of the extremities are cited in which after healing of the wound pressure upon the vessel at the point of suture would, as long as it was continued, obliterate the distal pulse. Bier's admirable essay is much more explicit than Lexer's forty-four operations cited by him for traumatic aneurism of from eight days' to three months' duration which included two aneurisms of the subclavian artery above the clavicle and two of the same vessel below that bone. He mentions the fact that the vessel did not participate in the formation of the aneurism and that bleeding would still continue from the damaged vessel even after compression was made on either side of the perforation. Whenever possible Bier recommends strongly the excision of the damaged portion of the lacerated vessel, together with the ligation of the divided ends of the artery reinforced by overlying suture when those ends are imbedded in reparative tissue. He carefully avoids the sacrifice of all neighboring branches. In no instance was there interference with the distal circulation. The adequacy of the collateral circulation could readily be determined by releasing the constricting tape on the distal side of the aneurism and observing whether blood escaped from the end of the divided artery while proximal compression was still employed. Lexer and several others also call attention to this valuable test. If the collateral circulation is found to be sufficient, ligature of the divided ends of the artery is preferable to suture. The four subclavian aneurisms were treated by ligation of the vessel on either side of the aneurism with tampanode of the cavity of the sac. Of these two died, one from sepsis, the other from a thrombus extending up the adjacent common carotid and interfering with the cranial circulation. In the forty-four cases the vessel was repaired in thirty, fifteen by lateral suture, and fifteen by end-to-end anastomosis including three with an intervening saphenous segment. In the entire series there were two deaths, both occurring in subclavian aneurism as previously mentioned.

In the experience of Lexer and Bier, although the number is small the operation for traumatic subclavian aneurism shows a very high mortality. An even higher mortality is mentioned by Braithwaite, who reports that "of twenty-eight recorded cases of penetrating and perforated injuries of the subclavian vessels, in nearly all of which both the artery and vein were involved, in the few in which an attempted excision was made, a fatal issue resulted on the table in every case." Furthermore, of the three cases reported by the writer, of which two had been in his care prior to operation by another surgeon, two died within twenty-four hours after the operation from excessive hæmorrhage. In the one that survived the symptoms of a cerebral embolus that permanently weakened the right upper extremity, immediately followed the operation and before the wound had entirely healed the physical signs of an extensive pulsating aneurismal varix developed at the site of the original aneurism. The operation in this patient is said to have lasted nearly five hours.

Hotz, quoted by Lexer, refers to the occasional persistence of cyanosis, coldness, and sensory disturbances after ligature of large arterial trunks and is an enthusiastic advocate of vessel suture, reporting six cases involving the common carotid, the axillary and femoral, in three of which repair by transplantation of the segment of the internal saphenous vein was done. In the carotid aneurism secondary hæmorrhage occurred requiring the ligation of the vessel on either side of the aneurism without subsequent disturbance of the cerebral circulation. Of the six cases none involved the subclavian vessels.

Zahradnecky, also quoted by Lexer, has collected 420 cases of traumatic aneurism treated either by ligature or by suture. Of the former, 11.6 per cent. developed gangrene; of the latter, only 3.8 per cent. developed gangrene. The mortality was 7 per cent. and 7.7 per cent. respectively. He emphasizes the advantages of early operation in cases closed by suture, recommending that it be done between the third and sixth week. He prefers ligation where adequate collateral circulation can be demonstrated, especially in the presence of infection. His individual experience comprises fifty-two cases, of which three recovered spontaneously. Of the remainder, twenty-eight were treated by ligation and twenty by suture. The cases treated by ligation included two of the subclavian, the result of the treatment of which is not mentioned. In six seriously septic cases gangrene developed with a fatal termination in five. Of the twenty cases treated by suture, thirteen were treated by lateral suture, five by circular end-to-end anastomosis and two by the transplantation of a segment of a vein. In an aneurism of the subclavian artery treated by end-to-end anastomosis, four centimetres of the artery being removed, the patient died of "anæmia." The two venous transplantations were done in the external iliac. Gangrene developed in each instance with a fatal termination.

It is perhaps well to emphasize that the operative treatment of spontaneous subclavian aneurism differs from that of the traumatic variety. Proximal ligation is in the former variety the operation of choice, supplemented by subsequent distal ligation with or without excision of the sac if the primary operation has been unsuccessful. In aneurisms of the first portion of the vessel ligation of the innominate must be done. In aneurisms of the second or third portion the ligation of the first part of the artery may be supplemented by ligation of the internal mammary and thyroid axis. If the artery proximal to the aneurism is atheromatous distal ligation as close as possible to the aneurismal sac is justifiable. Pearson, in a case of this kind, permanently cured an aneurism of considerable size by this procedure after an attempt to ligate the first part of the artery disclosed an extensively sclerotic condition in which the artery was adherent to its sheath, and to the cervical plexus.

The exposure of the innominate or of the first part of the subclavian is facilitated by the resection of the inner end of the clavicle with or without the adjacent part of the manubrium of the sternum. In the ligation of the deeper part of the left subclavian a satisfactory exposure of the vessel can be secured through the posterior mediastinum.

All kinds of absorbable and non-absorbable material including chromic gut, silk, kangaroo tendon, linen bands, fascial strips, together with special clamps such as those devised by Halsted, have been used in different varieties of ligation with equal success. The form of knot has also varied, the double ligature being favored. Successful ligation of the abdominal aorta is still relatively an unsolved problem. The patients of Hamann, who used braided silk, and of Vaughn, who used tape, survived the operation and lived for six months and two years respectively. At present fascial strips, especially in the ligature of large vessels, are generally preferred. Campbell, who has used this material in the ligation of the common carotid in three instances and of the popliteal in one, states that "simple ligation and treatment by other methods has not given nearly such good results in my hands or in the hands of my colleagues."

The operative treatment of traumatic subclavian aneurism consists in the exposure and temporary constriction of the artery both proximal and distal to the aneurism. On the right side the first part of the subclavian, or, if necessary, the innominate can be exposed through a resection of the inner end of the clavicle and adjacent manubrium as in the operation for spontaneous aneurism. The first part of the axillary is readily accessible after separation of the pectoralis major and inner edge of the deltoid above the tendon of the pectoralis minor. The clavicle is now sown across along the inner margin of the trapezius attachment and reflected downward after division of the sternocleidomastoid tendon. This gives an excellent exposure of the scalenus anticus and of the artery on either side of it together with the brachial plexus above it. Whether ligation of the two ends, after excision of the intervening segment is carried out or some form of suture or anastomosis is done, is then determined by the test already described. If infection is present or likely to develop, or if, in a perfectly clean wound the collateral circulation proves adequate, ligation must be the operation of choice. If suture or anastomosis is attempted, the ligature on either side of the sutured artery should be left *in situ* untied. If secondary hæmorrhage occurs satisfactory and immediate hemostasis can be effected by the tightening of these ligatures.

Operations for traumatic aneurism involving the first part of the left subclavian artery are extremely difficult. The choice between the anterior or posterior approach through which a ligature can be placed around the artery distal to its origin from the arch but proximal to the aneurism depends upon its relation to the aneurismal swelling as shown by the X-ray. The placing of the distal ligature presents no special difficulty. It is in this

variety of intra-thoracic aneurism that Bier suggests the tamponade of the aneurismal sac after ligatures on either side have been inserted and tightened.

The great risk of this operation, even in the absence of infection and in the absence of plexus complication, perhaps justifies conservative treatment. In Case III it was the intention of the writer to ligate the first part of the right subclavian artery within six or eight weeks after the trauma if by that time the aneurism had persisted or increased in size and to supplement it later on, if necessary, by ligation of the first part of the axillary. In Case IV ligation of the third part of the subclavian supplemented if necessary by ligation of the axillary distal to the aneurism was about to be carried out when the patient insisted on leaving the hospital. In Case V which, at no time, was seen by the writer, preliminary or actual ligation of the artery on either side of the stab wound might have averted a fatality.

The resection of the clavicle in these operations does not impair the ultimate strength of the shoulder girdle or prevent the return of the patient to laborious occupation. Even non-union or a subsequent osteomyelitis with necrosis extensive does not seem to interfere with the return of permanent strength in the upper extremity.

CASE I.—Spontaneous aneurism of the third part of the right subclavian reported by the writer in 1912.

CASE II.—Reported by Doctor Colp; referred to by the writer.

CASE III.—Adult, aged thirty years. Admitted to the Knickerbocker Hospital in May, 1931, with a bullet wound over the middle of the right clavicle from which there had been extensive hæmorrhage. He was transfused several times. Two days afterward when first seen by the writer the patient was in good condition. At that time a soft blowing murmur was heard at the junction of the middle and outer third of the clavicle and also above the bone. There was a weakness but no actual paralysis of the muscles of the right upper extremity with complete absence of sensation in all the fingers of the right hand. Ten days later both the muscular weakness and the loss of sensation had disappeared. The murmur loudest over the site of the wound was transmitted along the right subclavian and the right common carotid as far as the thyroid cartilage. There was expansile pulsation above the middle of the clavicle which was circumscribed with an infraclavicular thrill most pronounced below the middle of the bone.

During the following four weeks both murmur and thrill decreased markedly in intensity and extent. He complained of inability to regain his strength and is still underweight. During the following month these symptoms continued to improve including the expansile pulsation. The patient then passed into the hands of another surgeon who performed an immediate operation in another hospital. When seen by the writer four months after the injury and about two months after the operation, an operative scar was found extending from the junction of the third right costal cartilage and the sternum upward and outward along the sternomastoid attachment on the clavicle and then downward and outward to below the level of the pectoralis major one inch from the deltoid. In the upper concavity of this scar was a swelling three inches in diameter, having expansile pulsation and an extensive typical rasping murmur generally found in arteriovenous aneurisms. This is transmitted along both carotids to the skull and over the left side of the chest. It is also heard over the inferior angle of the scapula in the back. For two weeks after the operation patient states that he had paralysis of the left side which responded to electrical treatment. He still complains of weakness and numbness of the left leg and arm and of the left side of the neck, ear and scalp.

Six months later these various symptoms are somewhat more advanced and the patient is unable to do any heavy work.

CASE IV.—This patient was admitted to the Knickerbocker Hospital in July, 1930, with a stab wound over the upper part of the deltoid muscle. The healing of the wound was complicated by the discharge of a considerable amount of clotted blood, although no symptom of aneurism was noticed. Two months later, returning for observation, a pulsating swelling with a murmur extending down along the axillary artery was noticed and the patient was admitted to the hospital for operation. Becoming dissatisfied, he left the hospital voluntarily and after entering one of the city hospitals was operated on without delay. Evidently the operation consisted in some effort to reëstablish arterial continuity. The patient died in less than twenty-four hours after the operation chiefly from the loss of blood sustained.

CASE V.—Patient admitted to one of the city hospitals some years ago with a stab wound over the right clavicle, in which the symptoms of a pulsating swelling are said to have rapidly developed. In an operation to reëstablish arterial continuity, the patient lost so much blood from the rupture of the sac that he died within twenty-four hours.

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SURGICAL TREATMENT OF POST-OPERATIVE SAPHENOUS THROMBOPHLEBITIS

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So simple and so obvious is the idea presented in this paper that it well may seem to be saying an undisputed thing in a very solemn way, nor can the first blush of originality be urged as an excuse since Homans[1] has already brought the same idea before this Association. Nevertheless, although many surgeons in private conversations have advanced no objection to the desirability of ligating thrombosed peripheral veins that develop after operations, they apparently are reluctant to put the idea into practice. It is in the hope of persuading others to carry the principle into actual effect that this paper is written. As a basis for the argument a few brief case reports will be presented.

Case I.—Male, fifty-one years old, Union Memorial Hospital, No. 17679. Operated upon by the writer for left inguinal hernia, May 8, 1930, Dr. J. S. Davis removing a painful callus from the left foot at the same time. Uneventful convalescence until the ninth day, when there developed pain in the left calf, elevation of temperature to 100° and a palpable, hard, tender vein. *Diagnosis.*—Thrombophlebitis in a branch of the saphenous vein. An ice bag was applied to the leg and rest in bed continued beyond the usual time for convalescence from such an operation. The patient was allowed to go home on the nineteenth day after operation, under protest, because of his urgent insistence on leaving. Temperature at that time was practically normal and the pain had disappeared. The next day a definite, small, pulmonary embolus occurred with a distinct area of infarction. Patient recovered without further incident.

Case II.—Female, fifty-three years old, Union Memorial Hospital, No. 7109. Operated upon by the writer for cholecystitis and cholelithiasis November 27, 1929. Temperature gradually declined after operation but not quite to normal. On the fourteenth day there was pain in the left leg, rise of temperature to 100.2°, palpable, tender, saphenous vein. Temperature continued to rise to 103°. Pain and tenderness and palpable cord advanced day by day to the groin in spite of ice bags, slight elevation of leg and rigid confinement to bed. The whole leg became swollen. Condition gradually improved until by the thirty-eighth day the swelling and pain had largely subsided, the temperature was practically normal and the patient was allowed up in a chair. She was considered nearly ready to go home when a sudden and fatal pulmonary embolus occurred on the forty-third day after operation.

Case III.—Reported by Bunn.[2] The patient, a woman of fifty-five years, had recent injection treatments with a sugar solution for varicose veins. Following the treatment she developed a soreness along the course of the long saphenous vein and two attacks that were regarded as clearly due to pulmonary embolism. "Plans were being made to tie off the saphenous vein as soon as the patient's condition justified manipulation." The next morning, however, a final and fatal embolus occurred, the consultant actually hearing what he believed to be the sounds made by the passage of the embolus through the heart.

Case IV.—Reported by Freeman.[3] A woman of sixty-one years with varicose veins developed thrombophlebitis in the left saphenous vein. Under rest and hot packs for

five days the condition apparently improved greatly and the patient was allowed up in a chair. She developed a sudden dyspnœa and cyanosis and died in a few minutes. Autopsy revealed a long thrombus in the pulmonary artery regarded as a cast of the saphenous vein. The femoral and iliac veins and the vena cava were found normal at autopsy, the only vein involved being the saphenous.

Doubtless an extensive search for similar cases would bring to light many instances of embolism originating with thrombophlebitis of the saphenous veins but these four cases, all occurring in the past two or three years, are ample to prove the possibility of such grave accidents taking place. To argue that thousands of instances of thrombophlebitis occur without embolism is beside the point. The point is that embolism—rarely, to be sure, but none the less definitely—may convert a relatively simple situation into a dangerous or fatal one. We have been urged not to be satisfied with the ninety-nine good results but to struggle for the salvation of the hundredth case. Here is an opportunity to practice that doctrine. The ease and safety with which embolism may be guarded against when the original thrombus is limited to the saphenous system of veins is another strong reason for active intervention rather than the passive attitude now customary. Under local anæsthesia it is an extremely simple matter to ligate the saphenous in the thigh an inch or two below its entrance into the femoral. Such a procedure takes only a few minutes, causes very little pain and can be done even if the patient is extremely ill without adding appreciably to his burdens. The writer has been content to doubly ligate the vein with fine silk *in situ*, without dividing it, as a measure to prevent the occurrence of emboli. This, of course, can be done only before the process of thrombosis has spread entirely through the course of the saphenous and into the femoral—as did happen in the second case cited above. When the extent of the thrombophlebitis in the superficial vein is limited, it is not a great addition to the operation to excise the whole involved area and this would seem a step toward the quicker and more complete recovery of the patient.

The following cases may be cited to illustrate the execution of the plan advocated in this paper.

Case A.—Female, thirty-eight years old, Church Home and Infirmary, N. S., No. 328. Automobile accident with fracture of pelvis and ribs, cranial contusions, *etc.* During convalescence, after being in bed about six weeks, the patient developed pain, tenderness and a palpable cord on the inner side of the left calf with a slight elevation of fever (99.5)°. The thrombosis spread slowly and in about four days reached to and a little above the knee. The patient, who was a surgical nurse in charge of an operating room, was advised to have the vein ligated and the reasons for this explained. She accepted and the operation was carried out under local anæsthesia. The saphenous was ligated below Scarpa's triangle but the thrombosed portion was not removed. Healing was *per primum*, there was no addition to the time the patient would have been confined to bed, even if the ligation had not been done, and recovery was complete.

Case B.—Female, sixty-nine years old, Church Home and Infirmary, N. S., No. 583. The patient was recovering from a one-stage abdominoperineal resection of the rectum and sigmoid, done by the writer on June 20, 1931. On the seventeenth day after operation she began to have pain in the calf of the left leg and a hard, tender cord could be

felt in the position of the internal saphenous branch below the knee. The process spread slowly upward to the knee and on the twenty-first day after operation—the fourth day of the thrombotic process—the saphenous was ligated under local anæsthesia below Scarpa's triangle. The patient made an uneventful subsequent recovery and is still living and well.

Case C.—Female, forty-three years old, Church Home and Infirmary, N. S., No. 1618. The patient was on the service of Dr. Guy L. Hunner, who had performed a right nephrectomy on November 24, 1931. She was recovering well when, about three weeks after the operation, she developed a thrombophlebitis of the lower portion of the left long saphenous vein close to the internal malleolus. Doctor Hunner was good enough to ask me to see her because of my interest in such cases. The area of involved vein was small, being about four centimetres in length. The patient was advised to have the whole involved segment of vein resected. This was done under local anæsthesia and recovery took place without further incident.

These few cases are recorded, not, of course, to serve as the basis for any generalization, but to illustrate the sort of situations in which surgical interference may be called for. It is the writer's strong conviction that such surgical intervention is not only justifiable but highly desirable. It is difficult to see any real argument against it and there are obvious good reasons for it. The comparative rarity of serious embolism from saphenous thrombosis is the probable explanation of the customary passive attitude on the part of the surgeon. When attention is called to the existence of such a danger and the simplicity of the measures necessary to avert it, there would seem no objection to a revision of our usual "laissez faire" position and the assumption of a more direct intervention.

The subject of this paper restricts its proper field to consideration of thrombophlebitis occurring in the saphenous veins only and as a post-operative complication. There are, however, two extensions of the idea that should be discussed briefly. What has been said applies with equal force to the much more rare thromboses of other superficial peripheral venous systems as those of the arm for instance. When one comes to deal with the deep pelvic veins, however, the situation is distinctly different. Here the approach to the diseased vessel is a much more formidable procedure. The exact location of the trouble may be in itself a problem. The question of anæsthesia is by no means simple. On the other hand, deep pelvic thrombosis is far more common as a post-operative complication than is the similar process in the saphenous system and is probably the principal cause of embolism after operation. The writer believes that serious thought should be given to the question of direct surgical intervention in such cases. The day may come when we shall regard them also as suitable for prophylactic ligation of the thrombosed veins.

A second enlargement of the theme of this paper would take into its scope thrombophlebitis developing in conditions other than post-operative. The writer has applied the idea in a woman late in pregnancy with an extensive saphenous thrombosis. Her obstetrician was concerned lest the struggles of labor should dislodge the clot, and agreed to operative treatment. In this

instance the saphenous was ligated as usual and then the whole thrombosed segment of vein was dissected out. The patient went through her delivery without difficulty. Homans,[1] in the paper referred to earlier, advocating the ligation and excision of thrombosed varicose veins, refers to a similar case. This woman, four months pregnant, had already had evidence of multiple, small, pulmonary emboli. Thrombosed veins were removed from the leg under local anæsthesia, the emboli ceased and the pregnancy continued undisturbed. It would seem, therefore, that saphenous thrombosis during pregnancy presents another indication for ligation of the veins. But if the reasons be sound for intervention when veins become thrombosed after operation or during pregnancy, why not apply them to peripheral thrombophlebitis generally? Why put people to bed for weeks, on a passive or expectant form of treatment, when there is always the possibility of a clot getting loose? The two cases cited from the literature earlier in this paper prove that this possibility does at times actually happen. When a patient presents himself for treatment with thrombosed veins in his leg, why not perform the simple operation of ligation under local anæsthesia and eliminate the chance of embolism?

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AZYGOS VENOUS SYSTEM IN ITS RELATION TO SEPSIS

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In the following paper, I should like to call attention to a pathological and clinical condition, which, though apparently very unusual, may be much more common than is realized. By placing in the literature cases observed by me, and thus calling attention to this condition, perhaps other clinicians and pathologists may be reminded of similar cases, which they have seen and have had trouble in interpreting. As far as the literature is concerned, apparently nothing has been published on this subject.* One always hesitates to publish a clinical case *in extenso*, unless it illustrates a new clinical picture, especially before a society such as the American Surgical Association.

Case I.—Some years ago, a patient, a male of forty-one years, was seen by me suffering from varicose veins in the left thigh, with a thrombophlebitis in the left saphenous vein. The patient was running a mild temperature and physical examination showed a definite involvement of the left superficial saphenous system with gradual extension into the femoral and iliac veins on this side. His leg became swollen; blood culture was negative, though the temperature rose to over 103°. Within three weeks of the inception of the infection in the left saphenous vein, the condition extended well up into the trunk, so that the left lower extremity and the tissues of the trunk, particularly the left side of the trunk all the way up into the left axilla, were markedly swollen and œdematous. The right half of the body and the right lower extremity were not in any way affected. The urinary output remained quantitatively and qualitatively practically normal throughout. Towards the end of the third week, the patient began to have tenderness in the right calf, and as the œdema on the left side of the trunk and in the left axilla gradually disappeared, the right leg and thigh became swollen. By the end of the sixth week, the left side of the body had become absolutely normal, and a massive œdema had developed in the right lower extremity, right hip and abdominal wall up to the level of the umbilicus. The temperature still continued, pain was moderate. The temperature was remittent in character, suggesting a mild form of sepsis. Gradually, under rest in bed, elevation of the extremities and local ice applications, particularly at the beginning of the trouble over the femoral and iliac veins, complete recanalization took place, so that the patient, when he was seen seventeen years later, was in every way normal.

This peculiar clinical picture of a mild progressive thrombophlebitis with negative blood cultures, first involving the left side of the body up to the axilla and then the right side of the body up to the navel, presented a picture which was very difficult to interpret. At the time it seemed to me that one was forced to conclude that the patient had a persistent cardinal vein system, or, in other words, a double inferior vena cava, that the disease had extended up one side first, and then as the vein became recanalized, the process developed in the opposite femoral, and ascended up its iliac and its own inferior

* Since writing the above, A. S. Wischnevsky, from the Clinic of Professor Fedoroff, in the Zentralblatt für Chirurgie, p. 946, 1932, reports two cases of embolism through the azygos system, following spinal operations.

vena cava. Further consideration of the case in the light of the next patient to be reported *in extenso* has led me to revise the above opinion and conclude that the patient probably had an ascending thrombophlebitis from the femoral to the iliac and thence up the ascending lumbar and azygos minor system on the left side; and subsequently a similar process on the right side with involvement of part of the ascending lumbar and the azygos major, especially in the abdominal cavity.

Persistent double inferior vena cava I have never seen, and, as far as I know, no clinical or autopsy case has been reported. The clinical picture presented by the above unusual case would readily fit in with the second explanation as the azygos vein distribution, which is subject to great variation, may readily lead to such secondary superficial changes in the trunk as were observed in this case.

Case II.—About six years ago, a somewhat similar case was admitted to the Medical Service at Mount Sinai Hospital and gave the following history. A boy of twelve years, noticed five days before admission, after swallowing what apparently was a chicken bone, a sharp choking sensation, and pain in the right anterior chest, radiating to the axilla and scapula regions. The pain was increased by deep breathing, and apparently was very severe. For four days prior to admission, he had had dyspnœa and cough, and on the day of admission, a protracted severe chill with temperature to 104°. There was marked urinary frequency during the first days, as well as repeated sweats.

On physical examination, the patient was definitely very sick. There was some tenderness in the right flank and right axilla and spasm in the right upper quadrant of the abdomen. At the right base, there was some dullness and diminution in breath sounds, without any râles. There was shock tenderness over the liver. It was thought that the patient had a diaphragmatic pleurisy, but no pleural rub could be localized. The patient complained of some frequency of urination, but no definite renal pathology could be determined. His blood count was 12,800 white blood-cells, with 82 per cent. polymorphonuclears. The patient continued to run septic steeple-like temperature, ranging up to 106.8°, with a chill almost every day. Blood cultures were negative, as were Wassermann and Widal tests. On the second day after admission, a definite œdema was noted over the lower half of the right chest and the adjacent lumbar region. These areas were not particularly tender.

In view of the history of the onset, following the possible swallowing of a foreign body, an œsophagoscopy was done (Doctor Yankauer) and on the right lateral wall of the œsophagus at twenty-four centimetres a definite area covered with exudate was discovered. With the movement of respiration, it seemed as if pus exuded from this area, and it was thought that the patient had a posterior mediastinal abscess, for which surgical consultation was requested.

Fluoroscopical examination of the chest showed no evidence of mediastinal disturbance, and both leaves of the diaphragm, moreover, moved freely. Also progress of barium through the œsophagus was normal. Rectal examination was negative, except for slight tenderness high up, and this with tenderness over the liver and the violent septic febrile course, suggested the possibility of pyelophlebitis. The tenderness, which originally was rather diffuse over the right lower chest and upper abdomen, gradually became more localized over the right chest, and the œdema of the right chest wall persisted. Some tenderness developed over the sixth and seventh dorsal spines. With this, it was noted that on the right side a pleural rub developed over the right lower lobe where the breathing had become bronchovesicular and percussion note dull.

With the diagnosis of fluid in the right chest, an aspiration was performed fifteen days after admission, and purulent fluid withdrawn. During this period, the patient had several hemoptyses, and repeated chills and rapid loss of strength. He coughed up pieces of broken-down tissue, but no elastic fibres were identified. A second œsoph-

agoscopy gave the same findings, and biopsy showed inflamed mucosa. After the positive aspiration of the chest, signs of pyopneumothorax on this side became evident, and about this time signs of consolidation in the left lower lobe developed. An intercostal incision was made with drainage of pyopneumothorax. Culture of the fluid showed *Streptococcus hemolyticus*. The patient died shortly after operation.

The autopsy showed œdema of the right lower chest and an incision in the eighth intercostal space leading to a suppurative pleural cavity. On the left side, in addition, there was evidence of recent pleuritis. The lungs on both sides were covered with exudate from which *Streptococcus hemolyticus* was cultured and both lungs contained numerous small and large abscesses, many of which were on the surface. On the posterior wall of the œsophagus was a punched-out area one centimetre in diameter, which appeared to be a healing ulceration, in which a central perforation (biopsy?) was seen. The latter did not perforate the entire thickness of the œsophageal wall. There were several dilated veins in the submucosa. The vena azygos major underlying the area of ulceration contained an adherent thrombus two centimetres long, which was light brown in color and firm. Microscopical examination of the thrombus showed numerous chained streptococci and many groups of diplococci. In addition, the small veins of the submucosa of the œsophagus about the area of ulceration showed infected thrombi with infiltration of the wall of the veins. The posterior mediastinum was normal. In the pulmonary arteries there were numerous infected thrombi, and in the lungs there were many emboli with abscesses and pleuritis. No foreign body was found in the œsophagus. The hepatic and portal veins were negative, as were the rest of the autopsy findings.

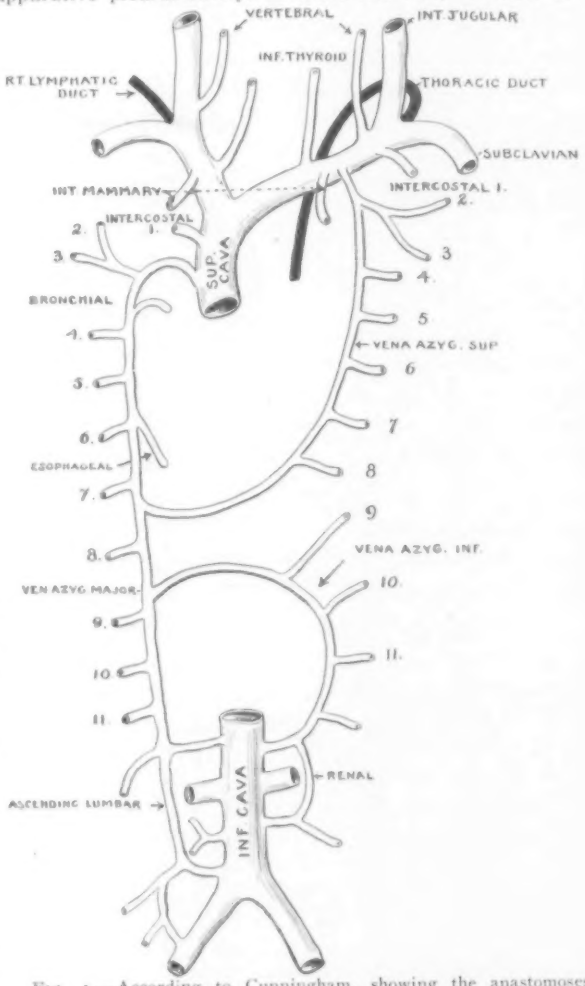

FIG. 1.—According to Cunningham, showing the anastomoses with the iliacs, inferior vena cava, lumbar, œsophageal, intercostal and bronchial veins.

Summary.—Following an œsophageal injury, the patient just reported developed ulceration in the lower end of the œsophagus with thrombophlebitis extending to the azygos major vein, which led to a disturbance in the return circulation in the right chest wall, producing an œdema and subsequently, as emboli were broken off and entered the superior vena cava and the heart, multiple abscesses developed in both lungs, which produced a secondary pleurisy in both right and left pleural cavities. The septic tempera-

ture with indefinite abdominal symptoms and tenderness over the liver had originally suggested the possibility of a portal vein thrombophlebitis, but the development of the localized œdema of the chest wall should have aroused the suspicion of an azygos vein thrombophlebitis, secondary to the ulceration of the œsophagus.

With such an array of symptoms as presented by both these cases, it seems that in the future it may be possible to recognize the clinical picture and possibly establish the diagnosis of the underlying pathology.

In conclusion, I would like to emphasize that in addition to the usual types of sepsis arising in the general circulation, in the portal circulation and

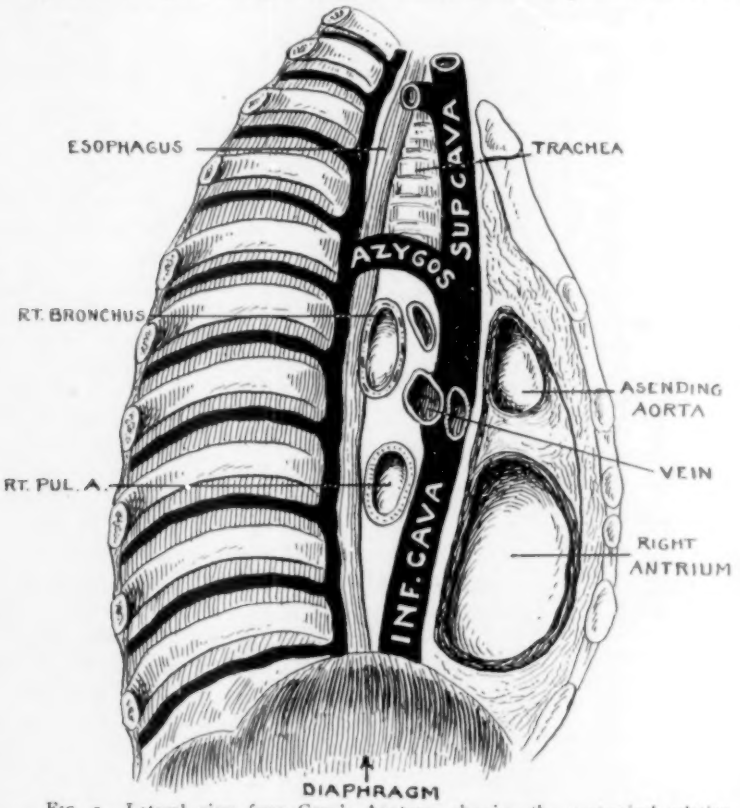

FIG. 2.—Lateral view from Gray's Anatomy showing the anatomical relation between the œsophageal and thoracic veins and azygos major system and anastomosis with the superior vena cava.

in the pulmonary circulation, in the future one must bear in mind the possibility of a sepsis originating in the heretofore disregarded subdivision of the systemic circulation, *i.e.*, in the azygos system of veins. To this description I add illustrations demonstrating the usual distribution of the azygos vein circulation, and their numerous anastomoses, as well as their relation to the abdominal organs and the thoracic organs, and in particular to the œsophagus, and the vertebral column. (Figs. 1 and 2.) I would not be surprised if the radicals of this system are more or less regularly involved in sepsis associated with osteomyelitis of the vertebral bodies, a case suggesting this combination having recently been operated upon on my service.

THE INTRAVENOUS INJECTION OF SCLEROSING SUBSTANCES

EXPERIMENTAL COMPARATIVE STUDIES OF CHANGES IN THE VESSELS

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The injection of varicose veins of the lower extremity with sclerosing agents has become very popular and has largely supplanted operative measures. Many thousands of injections have been made with a relative degree of safety, the incidence of dangerous sequelæ being very much lower than that following operative removal of the veins. The beneficial results obtained by the injection treatment are dependent upon changes in the vascular wall produced by the irritating agents, which in turn cause an obliteration of the dilated vessel. Obliteration of the vessel is accomplished largely by means of a thrombus, but also in part by a fibrosis which occurs in the wall of the vein. As a result of injury to the vein wall, especially in the presence of slowed circulation, as shown by Aschoff,[1] there occurs a deposition of platelets along the altered vessel wall with the formation of a fibrinous thrombus. In spite of the many injections which have been made with sclerosing substances in the treatment of varicosities of the lower extremity, relatively few histological examinations of injected veins have been made. In a still smaller group has a systematic comparative study of the changes which occur in the vein as a result of the intravenous injection of different sclerosing substances been made.

For the purpose of determining more accurately the changes which occur in veins following the injection with sclerosing agents and to compare the effect produced by many of the solutions now employed in the injection treatment of varicose veins, the present investigation was made. In order that carefully controlled observations might be made and as the study is largely a comparative one, the experiments were performed on animals, the dog being chosen as the animal for study. That the results obtained in the present investigation are not strictly applicable to the results which might be obtained in the clinic is self-evident, as the changes in a diseased vein, the contents of which are more or less stagnant, are undoubtedly greater than those which occur in a normal vein, the contents of which are in normal motion. Less marked changes following the intravenous injection of sclerosing agents should occur in the normal veins of the experimental animal than in the patient with varicose veins. That the incidence of thromboses is higher in clinical cases with varicosities is evident, because the slowing of the blood stream, shown by Magnus,[2] McPheeters and Rice,[3] Sicard, Forestier and Gaugier[4] to be present in varicose veins, permits the "eddying" of the blood stream, which, according to Aschoff,[1] favors thrombosis.

Twenty-seven dogs were used in the present investigation. Four hundred thirty-two injections were made in the twenty-seven dogs (four injections into the superficial veins of each leg). The internal saphenous vein was injected in the hind leg, the first

injection being made on the dorsum of the foot, the second on the anterior aspect of the ankle, the third on the dorso-lateral aspect of the leg, and the fourth on the posterior aspect of the knee. The antebrachial-cephalic vein (Ellenberger and Baum[5]) was injected in the foreleg, the first injection being made on the midportion of the dorsum of the paw, the second on the dorsum of the wrist, the third on the dorso-lateral aspect of the leg, and the fourth in the ante-cubital fossa. The same solution was used for all four injections in the same leg. Following the injections, the vein was compressed for approximately ten seconds, after which no compression was used. In two animals that received four injections of 0.04 cubic centimetre each of pure phenol, death occurred almost immediately after the injection. These two animals were discarded from the series. Three other animals died before any sections were removed. At autopsy immediately after death one section was removed from each extremity, so that four observations were made in each one of the three animals instead of the sixteen which had been planned. Two animals died after one group of sections had been removed and at autopsy another group of sections were removed so that from each one of these eight sections were obtained. This gives a total of 348 veins that were used for study.

The following substances with their respective doses were used for the intravenous injection: Dextrose, 50 per cent., one cubic centimetre; dextrose, 66 per cent., 1 cubic centimetre; invert sugar, 50 per cent., one cubic centimetre; invert sugar, 75 per cent., one cubic centimetre; invert sugar, 75 per cent., and saccharose, 5 per cent., ½ cubic centimetre; sodium chloride, 15 per cent., ½ cubic centimetre; sodium chloride, 20 per cent., ½ cubic centimetre; sodium chloride, 25 per cent., ½ cubic centimetre; sodium salicylate, 15 per cent., ½ cubic centimetre; sodium salicylate, 20 per cent., ½ cubic centimetre; sodium salicylate, 30 per cent., ½ cubic centimetre; sodium salicylate, 40 per cent., ½ cubic centimetre; sodium salicylate, 30 per cent., and sodium chloride, 10 per cent., ½ cubic centimetre; invert sugar, 50 per cent., and sodium salicylate, 10 per cent., ½ cubic centimetre; invert sugar, 75 per cent., and sodium salicylate, 20 per cent., ½ cubic centimetre; quinine and urea hydrochloride, ½ cubic centimetre; iodine, 1 per cent., and potassium iodide, 1 per cent., ¼ cubic centimetre; mercuric chloride, 1 per cent., 0.125 cubic centimetre; phenol, 1 per cent., ¼ cubic centimetre; and mercuric iodide, 1 per cent., 1/20 cubic centimetre. As mentioned above, in two animals very small doses (0.04 cubic centimetre) of pure phenol were used, but because it produced immediate death of the animal, it was discontinued. Pure phenol was employed because Dalton[6] strongly advocated its use in varicosities. Sections were removed after one-half hour, one hour, two hours, six hours, twelve hours, twenty-four hours, forty-eight hours, three days, four days, six days, ten days, fourteen days, twenty-one days, four weeks, six weeks, and eight weeks. Segments of veins were immediately fixed in 10 per cent. formalin solution and subsequently imbedded in paraffin. Hematoxylin and eosin, Mallory's connective tissue, and Weigert stains were made of the sections.

Each section was carefully studied histologically and changes occurring within the lumen and the various coats of the vessel were observed. The changes which occur in the endothelium, in the media and in the adventitia will be discussed separately. Some type of endothelial injury occurred in the majority of the sections examined. Of 348 sections examined, 259 (74.4 per cent.) had some type of endothelial injury. The greater number of changes were found in veins removed on or before the fourteenth day after the injection. (Table I.) Of 255 examinations made at the end of two weeks or earlier, in 224 (87.8 per cent.) there was some evidence of endothelial injury as contrasted with thirty-five (48.4 per cent.) in ninety-four observations made at the end of the third week or later. The substances which produced the highest incidence of damage to the venous endothelium were sodium salicylate, 40 per cent., and a solution of iodine, 1 per cent., and potassium iodide, 1 per cent. (Table II.) Other substances grouped in order of their deleterious effect on endothelium were sodium salicylate, 30 per cent., and sodium chloride, 10 per cent.; quinine and urea hydrochloride; and invert sugar, 75 per cent. and sodium salicylate, 20 per cent.

TABLE I

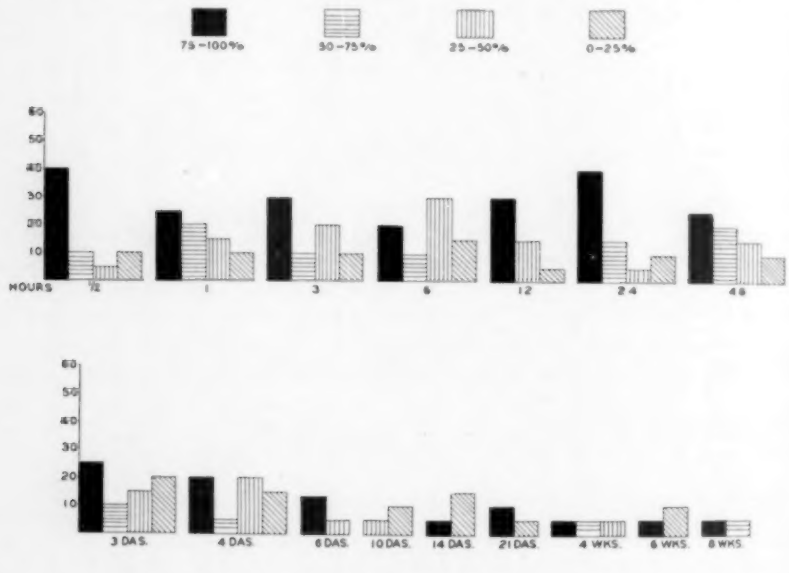
Summary of Changes Occurring in the Wall and the Lumen of Veins Injected with Sclerosing Agents According to the Interval Elapsing between Injection and Time of Observation

	ENDOTHELIUM															MEDIA					ADVENTITIA	COAGULA			
	DESTRUCTION					VACUOLIZATION					EXPOSURE OF NUCLEI														
	TOTAL	0-25%	25-50%	50-75%	75-100%	TOTAL	0-25%	25-50%	50-75%	75-100%	TOTAL	0-25%	25-50%	50-75%	75-100%	PROLIFERATION	EDEMA	LEUCOCYTIC INFILTRATION	HEMORRHAGE	MUSCLE HYPERTROPHY	CONNECTIVE TISSUE PROLIFERATION	DILATATION VASA VASORUM	TOTAL	FIBRINOUS	FIBROUS	CANALIZATION
1/2 hr.	75	20	5	10	40	45	0	5	25	15	50	15	5	20	10	0	100	0	0	5	0	20	30	30	0	0
1 hr.	75	15	15	20	25	45	5	30	10	0	45	5	5	25	10	0	100	5	0	30	0	60	10	10	0	0
3 hrs.	75	15	20	10	30	65	5	5	35	20	30	10	10	5	5	0	100	15	0	50	0	100	0	0	0	0
6 hrs.	75	15	30	10	20	55	15	15	20	5	35	20	0	5	10	0	100	20	0	80	5	100	5	5	0	0
12 hrs.	57.1	9.5	9.5	0	38.1	33.3	4.7	0	23.8	4.7	38.1	14.2	0	14.2	9.5	4.7	100	50	6.2	90	5	100	4.7	4.7	0	0
24 hrs.	75	15	10	15	35	60	5	15	20	20	20	5	5	10	0	0	100	40	0	75	0	85	10	10	0	0
48 hrs.	70	10	15	25	30	59.1	4.5	0	31.8	22.7	18.2	0	0	18.2	0	4.5	100	15	6.2	90	0	100	35	35	0	0
3 days	75	30	10	10	25	50	5	20	20	5	0	0	0	0	0	15	100	5	0	80	0	100	15	15	0	0
4 days	55	15	15	5	20	60	0	10	20	30	20	5	5	5	5	15	100	0	18.7	75	5.2	90	20	20	0	0
6 days	15	0	5	0	10	65	15	20	20	10	15	10	5	0	0	49	95	0	0	95	0	85	5	5	0	0
10 days	15	5	10	0	0	60	15	15	5	15	5	0	5	0	0	40	100	0	0	90	20	100	0	0	0	0
14 days	31.2	15.6	0	0	15.6	21.8	6.25	9.3	0	6.25	18.9	18.8	6.2	0	0	25	91.2	0	12.5	85	51.5	90	21.8	3.1	18.7	18.7
21 days	8	4	0	0	4	20	0	20	0	0	4	4	0	0	0	16	82.6	0	0	86.3	66.6	86.9	12	4	8	8
4 weeks	16.6	4.1	0	0	12.5	33.3	12.5	16.6	4.1	0	4.1	0	4.1	0	0	8.3	37.5	0	0	83.3	100	100	24.9	4.1	20.8	9.3
6 weeks	12.5	8.3	0	0	4.1	16.6	16.6	0	0	0	0	0	0	0	0	16.6	4.3	0	0	87.5	100	100	4.1	0	4.1	4.1
8 weeks	15	0	0	5	10	30	15	5	5	5	5	5	0	0	0	15	5	0	0	90	100	95	20	0	20	20

Endothelial Destruction.—Of 348 observations, there was some degree of endothelial destruction in 157 (45.1 per cent.). (Fig. 1.) Endothelial destruction was

FIG. 1.—(VV-311.) High-power photomicrograph of endothelium of vein injected four days previously with sodium salicylate, 40 per cent., showing complete destruction of endothelium with exposure of media to lumen of vessel.

observed most frequently in the veins removed on or before the fourth day. Of 181 veins extirpated on or before the fourth day, there were 129 (71.2 per cent.) with some



ENDOTHELIAL DESTRUCTION

GRAPH I.—Graphic representation of endothelial destruction occurring at the respective time intervals after the intravenous injection of sclerosing agents. The varying degrees of endothelial destruction are also shown.

TABLE II

Summary of Changes Occurring in the Vessel Wall and in the Lumen Following the Intravenous Injection of Sclerosing Agents

	ENDOTHELIUM																MEDIA					ADVENTITIA		COAGULA		
	DESTRUCTION					VACUOLIZATION					EXPOSURE OF NUCLEI															
	TOTAL	0-25 %	25-50 %	50-75 %	75-100 %	TOTAL	0-25 %	25-50 %	50-75 %	75-100 %	TOTAL	0-25 %	25-50 %	50-75 %	75-100 %	TOTAL INJURY	PROLIFERATION	EDEMA	LEUCOCYTIC INFILTRATION	MUSCLE HYPERTROPHY	HEMORRHAGE	CONNECTIVE TISSUE	DILATATION	COMBINED COAGULA	FIBRINOUS	FIBROUS	CANALIZATION
Dextrose 50%	27.7	22.2	0	0	5.5	61.1	16.6	11.1	16.6	16.6	22.2	0	16.6	5.5	0	72.2	11.1	81.2	11.8	70.5	0	29.5	88.2	11.1	11.1	0	0
Dextrose 10%	43.3	5.5	27.7	5.5	11.1	52.3	17.6	17.6	11.8	5.8	5.8	5.8	0	0	0	76.4	35.2	77.8	11.1	83.3	0	41.1	88.9	0	0	0	0
Dextrose 5%	25	18.7	0	6.8	0	55.5	0	16.6	22.2	16.6	33.3	11.1	5.5	16.6	0	72.2	5.5	82.3	5.8	70.5	6.2	16.7	88.2	0	0	0	0
Dextrose 25%	55.5	11.1	22.2	5.5	16.6	50	0	11.1	27.7	11.1	16.6	0	0	11.1	5.5	77.8	11.1	83.3	0	83.3	0	23.5	100	11.0	5.5	5.5	5.5
Dextrose 75%																											
Dextrose 5%	55.5	0	33.3	11.1	11.1	61.1	11.1	16.6	22.2	11.1	0	0	0	0	0	66.6	22.2	83.3	11.1	77.8	18.7	33.3	88.9	22.2	11.1	11.1	5.5
Sodium Chloride 1%	5.8	0	5.8	0	0	37.5	6.2	0	12.5	18.7	25	0	6.2	6.2	12.5	50	6.2	75	6.2	81.2	0	16.7	87.5	6.2	6.2	0	0
Sodium Chloride 2%	52.3	11.8	17.6	0	23.5	35.2	0	5.8	11.8	17.6	23.5	11.8	0	11.8	0	70.5	11.8	82.3	17.6	70.5	0	23.5	88.2	11.8	11.8	0	0
Sodium Chloride 5%	66.6	5.5	11.1	5.5	43.3	22.2	0	5.5	16.6	0	22.2	0	11.1	11.1	0	72.2	16.6	82.3	5.5	70.5	6.2	17.6	88.2	23.1	17.6	5.5	5.5
Sodium Salicylate 1%	23.5	23.5	0	0	0	29.3	5.8	11.8	11.8	0	29.3	29.3	0	0	0	64.7	0	76.4	5.8	82.3	0	35.2	88.2	0	0	0	0
Sodium Salicylate 2%	35.2	23.5	5.8	0	5.8	35.2	11.8	11.8	5.8	5.8	35.2	29.3	5.8	0	0	76.4	17.6	82.3	11.8	82.3	0	29.3	82.3	11.8	11.8	0	0
Sodium Salicylate 5%	61.1	16.6	5.5	22.2	16.6	55.5	11.1	16.6	11.1	16.6	5.5	0	0	0	5.5	77.8	11.1	88.9	0	88.9	0	25	94.4	16.6	11.1	5.5	0
Sodium Salicylate 10%	76.4	5.8	0	11.8	58.8	23.5	11.8	5.8	0	5.8	11.8	5.8	0.	5.8	0	88.2	11.8	82.3	17.6	70.5	0	37.5	100	47.0	23.5	23.5	23.5
Sodium Salicylate 30%																											
Sodium Chloride 10%	64.7	0	11.8	5.8	47.0	29.3	5.8	11.8	11.8	0	0	0	0	0	0	82.3	11.8	76.4	11.8	58.8	6.2	26.6	81.2	23.4	5.8	17.6	17.6
Dextrose 30%																											
Sodium Salicylate 10%	35.2	5.8	0	11.8	17.6	41.1	11.8	5.8	17.6	5.8	41.1	11.8	5.8	17.6	5.8	58.8	5.8	82.3	11.8	64.7	0	41.1	94.1	5.8	5.8	0	0
Dextrose 75%																											
Sodium Salicylate 25%	43.3	5.5	5.5	11.1	22.2	61.1	27.7	16.6	11.1	5.5	33.3	16.6	0	11.1	5.5	72.2	5.5	77.8	0	55.5	0	23.5	77.8	11.0	5.5	5.5	5.5
Quinine and Urea Hydrochloride 1%	66.6	0	11.1	5.5	50	22.2	0	11.1	11.1	0	0	0	0	0	0	77.8	16.6	77.8	27.7	52.9	6.2	37.5	83.3	28.4	11.8	16.6	16.6
Iodine 1%																											
Potassium Iodide 1%	41.1	29.3	5.8	0	5.8	47	11.8	17.6	5.8	11.8	17.6	11.8	0	5.8	0	88.2	17.6	82.3	0	76.4	0	29.3	82.3	11.8	11.8	0	0
Mercuric Chloride 1%	64.7	23.5	5.8	17.6	17.6	35.2	0	11.8	17.6	5.8	11.8	0	0	11.8	0	70.5	5.8	82.3	5.8	76.4	0	41.7	88.2	41.1	23.5	17.6	17.6
Phenol 1%	17.6	5.8	0	0	11.8	43.7	0	6.2	18.7	18.7	18.7	0	6.2	0	12.5	56.2	18.7	93.7	0	87.5	0	25	87.5	0	0	0	0
Mercuric Iodide 1%	27.7	11.1	0	0	16.6	50	5.5	11.1	16.6	16.6	22.2	0	5.5	5.5	11.1	72.2	16.6	72.2	11.1	77.8	0	29.3	83.3	5.5	5.5	0	0

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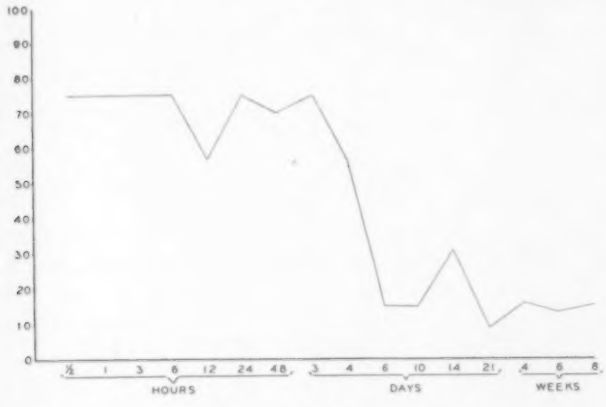
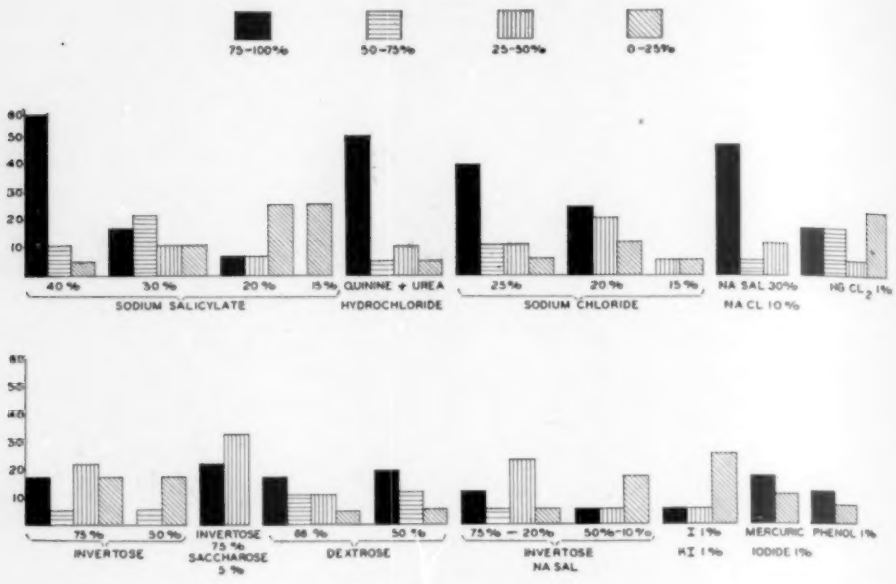
endothelial destruction, whereas of the 167 observations made on or after the sixth day, some degree of endothelial destruction was present in only twenty-eight (16.7 per cent.). (Graph I.) Undoubtedly, the endothelium in the veins examined after the sixth day had the same amount of trauma and a similar degree of destruction as was found present in the veins examined before the fourth day. In all probability, the difference in the amount of endothelial destruction observed before the fourth day (71.2 per cent.) and that observed after the sixth day (16.7 per cent.) is due to regeneration which occurred between the fourth and sixth days. (Graph II.) In the 181 observations made on or before the fourth day, a massive destruction of the endothelium ranging from 75 per cent. to complete destruction of the entire circumference of the vein was observed fifty-three times (29.2 per cent.), whereas in the 167 observations made on or after the sixth day, similar degrees of endothelial destruction were observed only fourteen times (8.3 per cent.). In only one group of all the observations made after the sixth day was the incidence of destruction of the endothelium higher than 16 per cent. Of the thirty-two veins examined fourteen days after the injection of the vein, there was no endothelial destruction in twenty-two (68.7 per cent.). In five (15.6 per cent.), the extent of destruction was graded as being less than 25 per cent. of the cir-



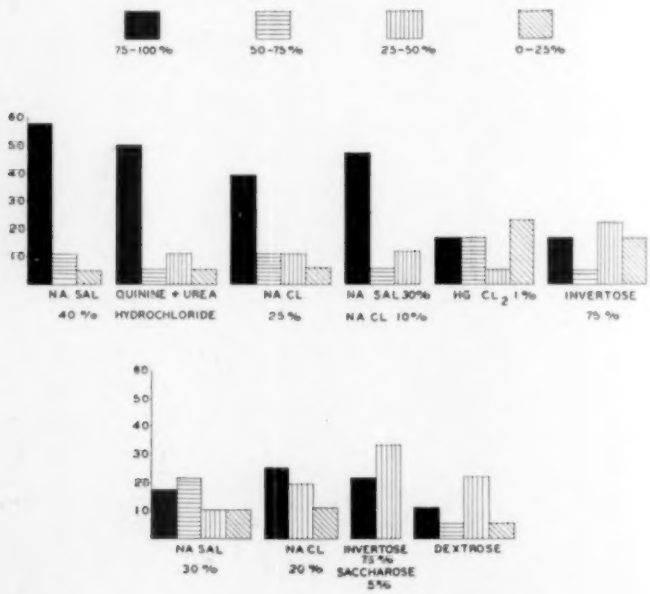
GRAPH II.—Graphic representation of combined amounts of destruction occurring in veins at various time intervals after injection with sclerosing agents.

cumference, whereas in five (15.6 per cent.), it was massive in that more than 75 per cent. of the entire endothelium was destroyed. In four of these, the endothelium was completely destroyed and the lumen filled with a dense organizing thrombus, which was adherent to the vein wall. Of the fifty-three veins removed on or before the fourth day with massive destruction of the endothelium (ranging from 75 per cent. to 100 per cent. of the circumference), in only seven (13.2 per cent.) was there a large thrombus, whereas in the fourteen veins removed on or after six days with a similar endothelial destruction, a large thrombus completely filling the vessel and firmly adherent to the wall was found in thirteen (92.8 per cent.). It is thus evident that the endothelium in most cases except those with massive thrombosis regenerates between the fourth and sixth days after the injection of the vein. The greatest amount of endothelial destruction resulted from the use of sodium salicylate, 40 per cent. Of seventeen observations, some endothelial destruction occurred in thirteen (76.4 per cent.). Of greater significance is that in ten (58.8 per cent.) instances, the endothelial destruction was classed as massive (ranging from 75 per cent. to 100 per cent.). The second most destructive agent was quinine and urea hydrochloride. Twelve (66.6 per cent.) of eighteen observations showed some destruction; in nine (50 per cent.) the endothelial destruction was classed as massive. The least destructive agent was sodium chloride, 15 per cent.;



GRAPH III.—Graphic representation of varying degrees of endothelial destruction produced by the intravenous injection of respective sclerosing agents.

in only one (5.8 per cent.) of seventeen observations was there any evidence of endothelial destruction and this was classed as ranging from 25 per cent. of the circumference of the vein. (Graphs III and IV.)



GRAPH IV.—Graphic representation of endothelial destruction produced by the ten most destructive of the twenty sclerosing agents employed, arranged in order of the amount of combined destruction.

FIG. 2.

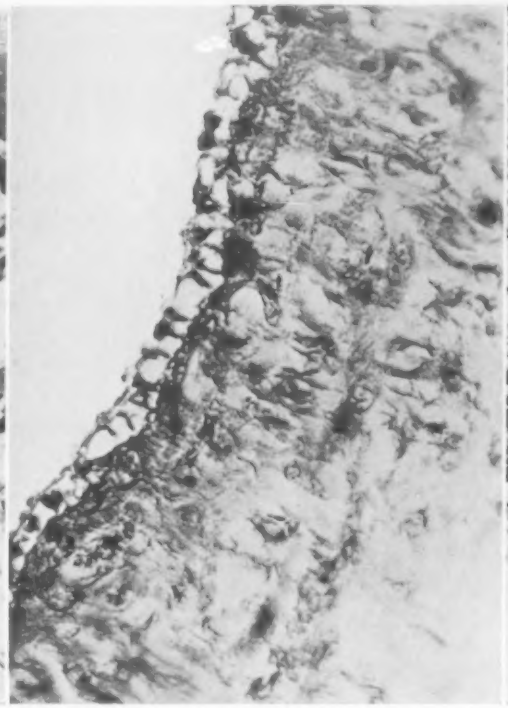


FIG. 3.

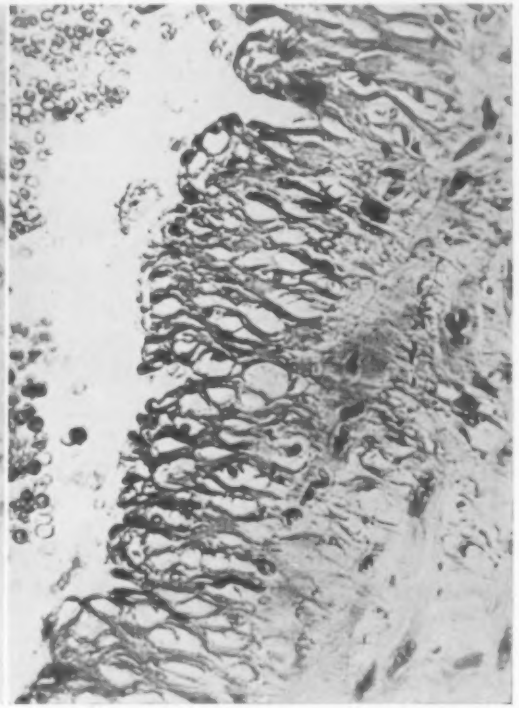


FIG. 4.

FIG. 2.—(VV-236.) High-power photomicrograph of vein injected twelve hours previously with dextrose, 50 per cent., showing partial destruction of cells of the endothelium in that the outer half of the cell is destroyed, leaving the nuclei exposed to the lumen of the vessel.

FIG. 3.—(VV-324.) High-power photomicrograph of vein injected four days previously with invertose, 50 per cent., and sodium salicylate, 10 per cent., showing vacuolization of the cells of the endothelium.

FIG. 4.—(VV-309.) High-power photomicrograph of vein injected four days previously with sodium salicylate, 20 per cent., showing marked proliferation of the endothelial cells.

In addition to endothelial destruction other changes frequently occurred in the intima; *i.e.*, partial destruction of the endothelial cell, so that the nuclei were not covered with cell membrane but were exposed to the vessel lumen and vacuolization of the endothelial cells. In sixty-six (18.9 per cent.) of 348 observations, there was evidence of the endothelial nuclei being "exposed." (Fig. 2.) This change was found in thirty-seven (37 per cent.) of 100 veins extirpated twelve or more hours after the injection, whereas in 248 veins removed after twenty-four hours, it occurred in only twenty-nine (11.6 per cent.). Of the sixty-six instances in which the nuclei were "exposed," thirty-seven (56 per cent.) occurred in veins removed on or before the twelfth hour. "Exposure" of the nuclei occurred most frequently in veins injected with invertose, 50 per cent., and sodium salicylate, 10 per cent.

In addition to the endothelial destruction and "exposure" of the endothelial nuclei, other changes occurred in the endothelium. A rather frequently observed change was vacuolization of the endothelial cells (Fig. 3) which occurred in 151 (43.3 per cent.) of 348 observations. Of 221 veins removed on or before the tenth day, there were 119 (53.8 per cent.) in which vacuolization of the endothelial cells occurred, whereas of 127 veins extirpated on or after the fourteenth day, there were thirty-two (25.2 per cent.) showing this change. The substances which produced the greatest degree of vacuolization were dextrose, 50 per cent.; invertose, 75 per cent. and saccharose, 5 per cent.; and invertose, 75 per cent. and sodium salicylate, 20 per cent. In each, the percentage of instances in which vacuolization was observed was 61.1 per cent. Strangely enough, the degree of vacuolization was least in those veins injected with the more destructive agents; *viz.*, sodium chloride, 25 per cent.; sodium salicylate, 40 per cent.; and quinine and urea hydrochloride. The percentages of observations showing vacuolization in each were 22.2, 23.5, and 22.2, respectively.

Proliferation of the endothelium; *i.e.*, heaping up of the endothelial cells so that the intima consisted of several layers, was not infrequently observed (Fig. 4). Of 348 veins, endothelial proliferation was observed in forty-five (12.9 per cent.). There was no evidence of endothelial proliferation observed within the first six hours following injection. Of the 181 veins removed on or before the fourth day, only eight (4.4 per cent.) showed evidence of endothelial proliferation, whereas of the 167 veins extirpated on or after the sixth day, thirty-seven (22.1 per cent.) showed evidence of endothelial proliferation. This finding corroborates the assumption made above that between the fourth and sixth days endothelial regeneration occurred.

Pyknosis of the endothelial nuclei was frequently observed. In 348 examinations, pyknosis of the nuclei was present in sixty-nine (19.8 per cent.). Of the 203 observations made on or before the tenth day, in seventeen (8.3 per cent.) and of the 145 observations made on or after the fourteenth day in fifty-two (35.8 per cent.) there was evidence of pyknosis of the endothelial nuclei. The greatest amount of pyknosis of the endothelial nuclei was observed in those veins injected with iodine, 1 per cent., and potassium iodide, 1 per cent.; sodium salicylate, 15 per cent.; and mercuric iodide, 1 per cent. The least amount of pyknosis occurred in those veins injected with the most caustic sclerosing agents, such as sodium salicylate, 40 per cent.; quinine and urea hydrochloride, and sodium chloride, 25 per cent. This was undoubtedly due to the fact that in these veins, because of the extensive destruction, no endothelium remained to show the less destructive changes.

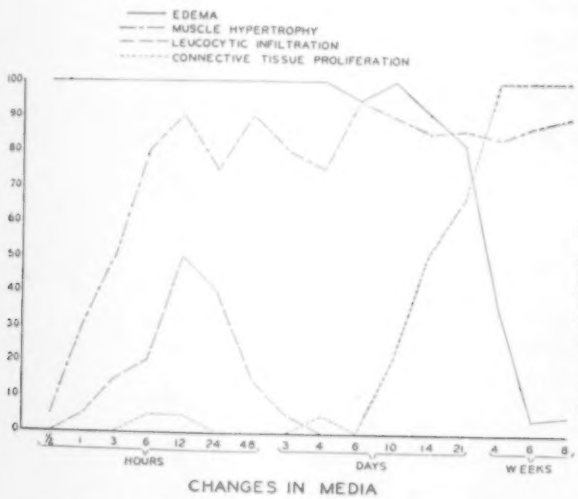
CHANGES IN THE MEDIA

Œdema.—One of the most frequently encountered changes in the media was œdema (Fig. 5), which occurred in 289 (83.7 per cent.) veins of 348 extirpated from one-half hour to eight weeks after the injection of sclerosing substances. Of 283 veins extirpated at the end of or before the third week following the injection, 278 (98.2 per cent.) had œdema, whereas of sixty-eight observations made four weeks or later after

the injection, there were only eleven (16.1 per cent.) with œdema. (Graph V.) All of the veins examined from one-half hour up to four days after the injection of the

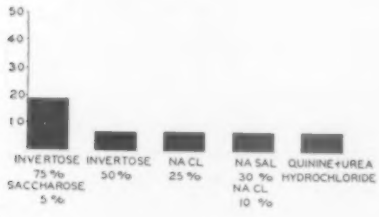
FIG. 5.—(VV-454.) High-power photomicrograph of media of vein injected six weeks previously with sodium salicylate, 30 per cent., showing marked œdema of the media producing separation of the muscle fibres as indicated by "A."

sclerosing substance showed some evidence of œdema. The œdema was most extensive forty-eight hours after the injection, at which time in 55 per cent. the œdema was classed as ++++, 30 per cent. as +++, and 15 per cent. as ++. Phenol, 1 per cent., produced œdema in the greatest number of instances; *i.e.*, in fifteen (93.7 per cent.) of sixteen observations. Mercuric iodide, 1 per cent., caused œdema in the fewest instances of all the substances investigated, it being present in thirteen (72.2 per cent.) of eighteen observations.



CHANGES IN MEDIA

GRAPH V.—Graphic representation of changes occurring in the wall of the vessel as a result of the intravenous injection of sclerosing agents.



HEMORRHAGE IN MEDIA

GRAPH VI.—Graphic representation of the percentages of observations in which hæmorrhage in the media was produced by the intravenous injection of sclerosing substances.

Changes in Muscle.—In twenty-four (6.8 per cent.) of the 348 veins, the muscle of the

media was either fully or partially destroyed. In twenty (5.7 per cent.), the destruction was complete, whereas in four (1.1 per cent.), it was partial. Four (25 per cent.) of the twenty instances of complete destruction of muscle occurred in veins injected with quinine and urea hydrochloride. Of the eighteen veins injected with this solution, complete or partial destruction of the muscle occurred in five (27.7 per cent.); in four (22.2 per cent.) there was complete destruction; and in one (5.5 per cent.) there was only partial destruction. Of seventeen veins injected with sodium salicylate, 30 per cent., and sodium chloride, 10 per cent., there were four (23.5 per cent.) instances of complete or partial destruction of the muscle. Of these three (17.6 per cent.) were complete and one (8.5 per cent.) was partial. Three (17.6 per cent.) of seventeen veins injected with sodium salicylate, 40 per cent., showed complete destruction of muscles. In a large number of observations, there was a suggestion of muscle hyperplasia. The finding was based upon an apparent extension of muscle fibres and bundles into the adventitia. (Fig. 6.) In 246 (70.7 per cent.) of 348 veins, there was definite evidence of muscle hypertrophy, as demonstrated by increase in the size of the muscle cells and

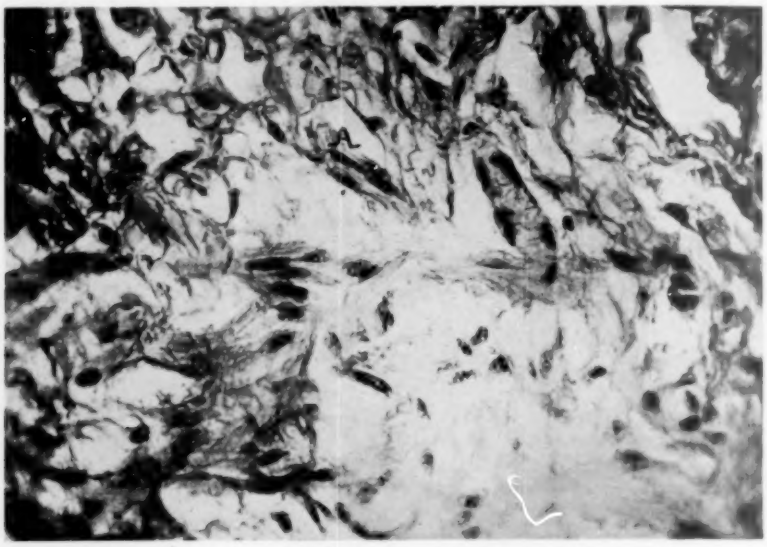


FIG. 6.—(VV-360.) High-power photomicrograph taken at junction of media and adventitia of vein injected ten days previously with invertose, 75 per cent., and saccharose, 5 per cent., showing extension of muscle bundles of media into adventitia as illustrated by "A."

bundles. (Graph V.) In the first one-half hour, hypertrophy occurred only once (5 per cent.) in twenty observations, whereas of the twenty observations made at the end of three hours, this was present in ten (50 per cent.). Seven (17.5 per cent.) of the forty observations made on or before the first hour, and 239 (77.6 per cent.) of the 308 observations made on or after the third hour showed muscle hypertrophy. The highest incidence of muscle hypertrophy occurred in veins injected with sodium salicylate, 30 per cent. (88.9 per cent.), and phenol, 1 per cent. (87.5 per cent.), invertose, 75 per cent. (83.3 per cent.) and dextrose, 66 per cent. (83.3 per cent.). The lowest incidence of muscle hypertrophy occurred in the veins injected with quinine and urethane, probably because of the extensive muscle destruction which resulted from the intravenous injection of this substance.

Leucocytic infiltration was demonstrated in thirty veins (8.6 per cent.). (Fig. 7.) Eighteen (63.4 per cent.) of the thirty veins were removed twelve and twenty-four hours after the injection. Of the forty veins extirpated twelve and twenty-four hours

after the injection with sclerosing agents, eighteen (45 per cent.) showed leucocytic infiltration. Of the 307 veins removed before the twelfth hour and after the twenty-

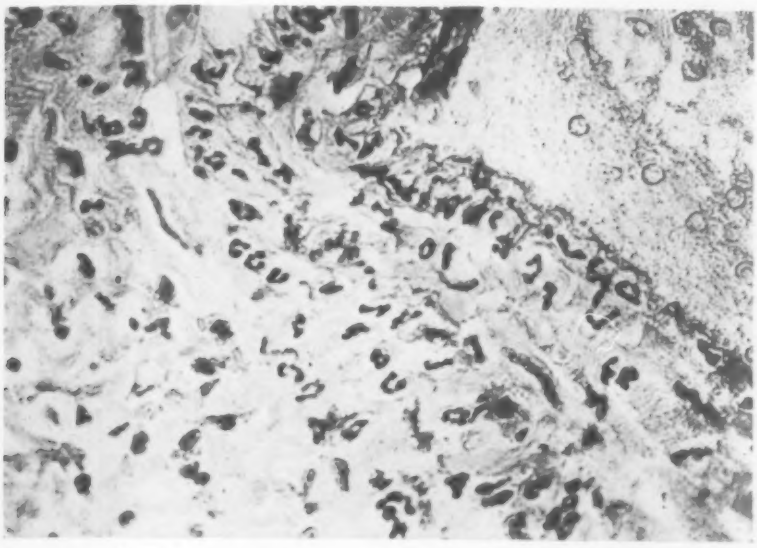


FIG. 7.—(VV-257.) High-power photomicrograph of vein injected twenty-four hours previously with dextrose, 66 per cent., showing leucocytic infiltration of the media.

fourth hour, only twelve (3.9 per cent.) had leucocytosis. (Graph V.) The leucocytic infiltration was greatest in those veins injected with quinine and urea hydrochloride.

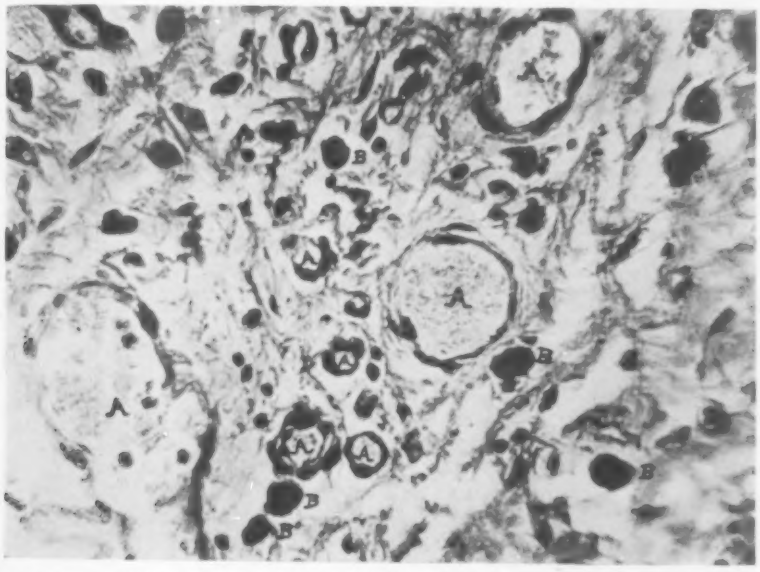


FIG. 8.—(VV-487.) High-power photomicrograph of thrombus in vein injected eight weeks previously with invertose, 75 per cent., showing recanalization of thrombus. Blood vessels indicated by "A" and phagocytosis of hemosiderin by endothelial cells by "B."

Five (27.7 per cent.) of the eighteen veins injected with this solution showed extensive leucocytosis. Seventeen and six-tenths per cent. of the veins injected with sodium

salicylate, 40 per cent., and sodium chloride, 20 per cent., showed a leucocytosis. Both mononuclear and polymorphonuclear cells were found in the exudate. There were also large numbers of endothelial cells. The number of polymorphonuclear leucocytes was never so great as that seen in bacterial inflammations. The endothelial cells showed evidence of phagocytosis and frequently were loaded with hemosiderin. (Fig. 8.)

In seven (2.01 per cent.) of the 348 veins, hæmorrhage was found in the media. (Fig. 9.) In two (28.5 per cent.) veins injected fourteen days previously, in three (42.8 per cent.) injected four days previously, and in one each injected twelve and twenty-four hours previously, there was hæmorrhagic infiltration of the media. (Graph VI.) Three (42.8 per cent.) of the veins with hæmorrhage had been previously injected with invertose, 75 per cent., and saccharose, 5 per cent. One vein each (14.2 per cent.) had been injected with invertose, 50 per cent.; sodium chloride, 25 per cent.; sodium salicylate, 30 per cent. and sodium chloride, 10 per cent.; and quinine and urea hydrochloride. In four (57.1 per cent.) of the seven veins in which hæmorrhage was observed, the substance used was invert sugar alone or combined with saccharose.

Fibrosis of the vein wall was frequently observed in the veins injected with sclerosing substances. Of 348 observations, in seven (2.1 per cent.) the wall of the

FIG. 9.

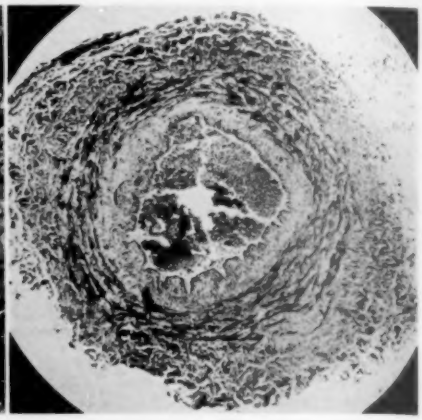


FIG. 10.

FIG. 9.—(VV-315.) High-power photomicrograph of media of vein injected four days previously with sodium chloride, 25 per cent., showing hæmorrhage causing wide separation of the muscle fibres of the media.

FIG. 10.—(VV-480.) Low-power photomicrograph (Mallory connective-tissue stain) of vein injected eight weeks previously with quinine and urea hydrochloride, showing fibrosis of the media with wide separation of the muscle bundles.

vein was so destroyed by the sclerosing substance that it could not be determined whether connective-tissue proliferation was present or not. Of the remaining 341, there was connective-tissue proliferation in 104 (30.5 per cent.). (Fig. 10.) There were only seven (3.5 per cent.) of the 200 veins injected within ten days and ninety-seven (67.5 per cent.) of the 148 veins injected fourteen or more days previously which showed evidence of connective-tissue proliferation. (Graph V.) Fibrosis of the media was found in all the veins injected four and six weeks previously. The greatest amount of fibrosis occurred in those veins (41.7 per cent.) which were injected with mercuric chloride, 1 per cent. In 41.1 per cent. of the veins injected with dextrose, 66 per cent.; invertose, 50 per cent. and sodium salicylate, 10 per cent., was there fibrosis. In 37.5 per cent. of the veins injected with quinine and urea hydrochloride and sodium salicylate, 40 per cent., fibrosis of the vein wall was observed. The earliest evidence of fibrosis was seen in a vein injected with sodium salicylate, 40 per cent.; three hours after the injection, there was noted a definite increase in the number of fibroblasts. Following the injection of invertose, 50 per cent., and sodium salicylate, 10 per cent., there was evi-

dence of connective-tissue proliferation as early as twelve hours and four days, respectively, after the injection. In those veins with thrombi, there occurred an early invasion of the thrombus with fibroblasts which progressed so that during the later periods (after eight weeks) it was frequently impossible to distinguish the vein wall from the thrombus. (Fig. 11.)

CHANGES IN THE ADVENTITIA

The most constant change observed in the adventitia following the intravenous injection of sclerosing substances was a dilatation of the vasa vasorum. In many instances, there was in addition to the dilatation evidence of new blood-vessel formation. Three hundred and seven (88.2 per cent.) of the 348 veins examined showed evidence of dilatation of the vasa vasorum. Ten (25 per cent.) of the forty observations made one-half hour and one hour, respectively, after the injection of the sclerosing substance, and 297 (96.4 per cent.) of the 308 observations made three hours or longer

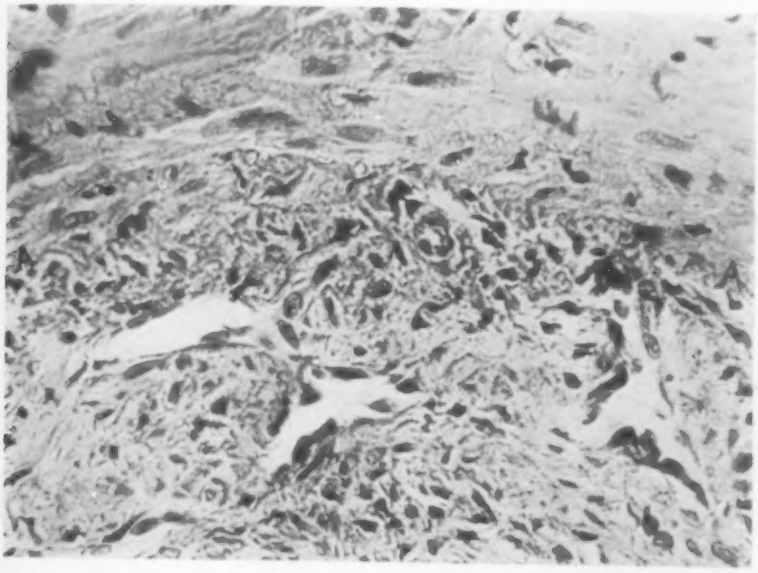
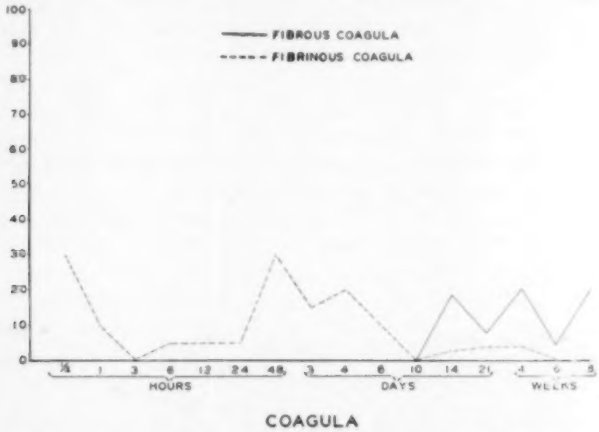


FIG. 11.—(VV-395.) High-power photomicrograph taken at junction between vein wall and organized thrombus in vein injected fourteen days previously with invertose, 75 per cent., and saccharose, 5 per cent., showing intimate attachment of thrombus to vein wall at "A."

after the injection of the sclerosing substance showed evidence of dilatation of the vasa vasorum in the adventitia. The most marked reaction as regards dilatation of the vasa vasorum was observed in those veins injected with sodium salicylate, 40 per cent., and invert sugar, 75 per cent. All the veins injected with these substances showed evidence of dilatation of the vasa vasorum.

Thrombi.—Thrombosis occurred in forty-six (13.2 per cent.) of the 348 veins examined. Of these, thirty-one (67.4 per cent.) were fibrinous and sixteen (34.8 per cent.) were fibrous. Fibrinous thrombi occurred in 8.9 per cent. of the 348 veins. The greatest number of fibrinous thromboses, as might be expected, occurred early after the injection of the sclerosing substances. Of the 181 veins examined on or after the sixth day, only five (2.9 per cent.) contained fibrinous thrombi. Of the thirty-one fibrinous thrombi, sixteen (51.6 per cent.) occurred in the sections removed on the second, third, and fourth days. These sixteen (20 per cent.) fibrinous thrombi occurred in eighty veins examined whereas only fifteen (5.2 per cent.) occurred in the remaining 268 veins. (Graph VII.) Those substances causing the greatest number of fibrinous

thrombi were sodium salicylate, 40 per cent., and mercuric chloride, 1 per cent. In both instances fibrinous thrombi developed in four (23.5 per cent.) of eighteen obser-



GRAPH VII.—Graphic representation of the percentages of observations made after the intravenous injection of sclerosing agents in which both fibrous and fibrinous thrombi were present.

vations. The thrombi developing in the veins injected with sodium salicylate, 40 per cent., were more extensive than those developing in the veins injected with mercuric chloride, 1 per cent. Organized thrombi were found in sixteen (4.59 per cent.) of the

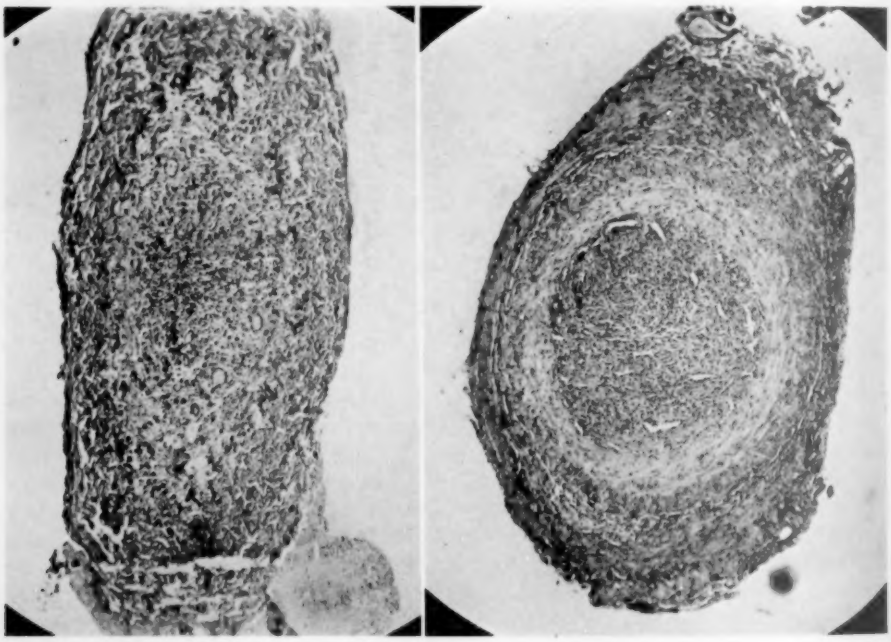


FIG. 12. FIG. 13.

FIG. 12.—(VV-487.) Low-power photomicrograph of vein injected eight weeks previously with invertose, 75 per cent., showing complete obliteration of lumen of vessel by organized thrombus. There are a large number of new blood-vessels in the thrombus and considerable deposition of hemosiderin.

FIG. 13.—(VV-395.) Low-power photomicrograph of vein injected fourteen days previously with invertose, 75 per cent., and saccharose, 5 per cent., showing complete obliteration of vessel with organized thrombus. There are a large number of newly formed blood-vessels in the thrombus.

348 veins. (Graph VII.) (Fig. 12.) All were in veins removed fourteen days or longer after the injection. Eleven (16.7 per cent.) of the fibrous thrombi occurred in those veins removed between two and four weeks inclusive after the injection. (Fig. 13.) The largest number of fibrous thrombi was caused by sodium salicylate, 40 per cent. (23.5 per cent.) of the veins injected with this substance. (Fig. 14.) Quinine and urea hydrochloride, sodium salicylate, 30 per cent., and sodium chloride, 10 per cent., each produced fibrous thrombi in three (17.6 per cent.) of seventeen veins injected. (Graph VIII.)

Canalization of the fibrous thrombi occurred in seventeen (94.4 per cent.) of the fibrous thrombi. (Figs. 8 and 11.) Canalization of the thrombus occurred most frequently in veins (23.5 per cent.) injected with sodium salicylate, 40 per cent. Canalization occurred in 17.6 per cent. injected with sodium salicylate, 30 per cent. and sodium chloride, 10 per cent.; and mercuric chloride, 1 per cent.; and in 16.6 per cent. of the

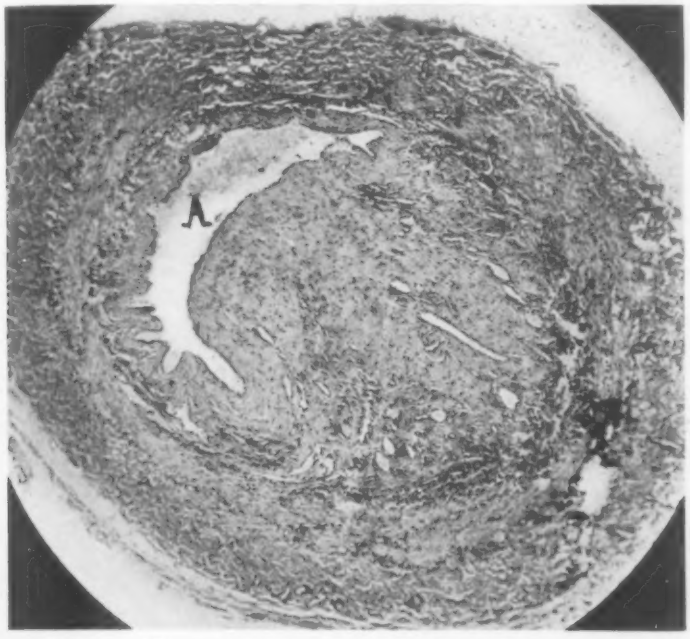
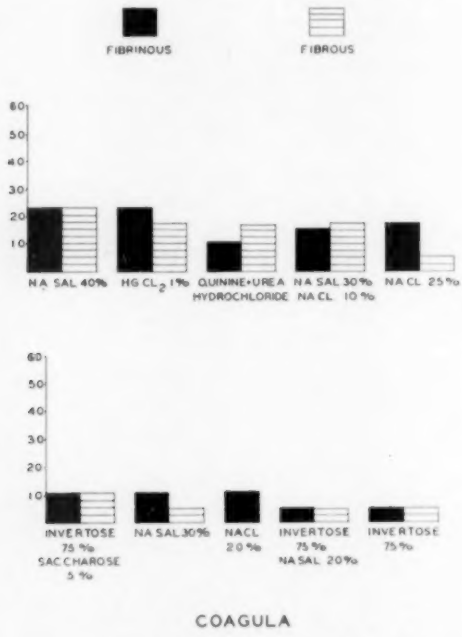


FIG. 14.—(VV-479.) Low-power photomicrograph of vein injected eight weeks previously with sodium salicylate, 40 per cent., showing almost complete obliteration of the lumen of the vein with organized thrombus. At the extreme left, as indicated by "A," is the original lumen of the vein.

veins injected with quinine and urea hydrochloride. There was no evidence of canalization on or before the tenth day, whereas all the cases in which canalization occurred were observed on or after the fourteenth day.

Comment.—As a result of intravenous injection of sclerosing agents, extensive changes occur in the wall of the vessel. The changes which occur in the vein wall may be considered as destructive and reparative. As might be expected, the endothelium is considerably altered. The results obtained by other investigators have not been consistent. Only partial destruction of the endothelium was observed twenty-four hours after the injection of sclerosing substances by Bazelis,[7] Meisen,[8] Hanschell,[9] and Howard and his co-workers.[10] On the other hand, Regard[11] and Schwartz[12] observed destruction of the endothelium within twenty-four hours, whereas Kern[13] and

Wolf,[14] whose examinations were made after forty-eight hours, report complete destruction of the endothelium. That the difference in the results obtained by these earlier investigators is due to the use of different solutions is possible, even though Meisen[8] employed sodium salicylate, 40 per cent., as a sclerosing agent. This contention is substantiated by the results obtained in the present investigation in which it is found that the degree and extent of vascular change depend to a great extent upon the particular sclerosing agent employed. The extent and degree of endothelial destruction varied considerably according to the substance used. However, definite changes in the vein occurred within one-half hour after injection of the sclerosing substances; *i.e.*, 75 per cent. of the veins injected one-half hour



GRAPH VIII.—Graphic representation of the percentages of both fibrous and fibrinous thrombi produced by the respective sclerosing agents, arranged in order of their efficacy in the production of thrombi.

previously showed some evidence of endothelial destruction. (Chart I.) The incidence and extent of the endothelial destruction were classified as follows: seventy-five per cent. to complete destruction, 40 per cent.; 50 per cent. to 75 per cent., 10 per cent.; 25 per cent. to 50 per cent., 5 per cent.; and 0 to 25 per cent., 20 per cent. Veins injected one-half hour previously with sodium salicylate, 40 per cent.; sodium salicylate, 30 per cent. and sodium chloride, 10 per cent.; invert sugar, 75 per cent. and saccharose, 5 per cent.; and phenol, 1 per cent. showed complete destruction of the endothelium. Those veins injected with dextrose, 66 per cent.; sodium chloride, 20 per cent.; sodium salicylate, 30 per cent.; invert sugar, 50 per cent. and sodium salicylate, 10 per cent. had a destruction of the endothelium which

was classified as from 75 to 100 per cent. of the circumference of the vein. It is thus apparent that the more caustic solutions exert a destructive effect upon the vascular endothelium immediately or at least within one-half hour's time after the intravascular injection. The number of veins with endothelial destruction at the end of one-half hour was the same as those with endothelial destruction at the end of twenty-four hours, in each 75 per cent. Our results substantiate the findings of Wolf,[14] that following the intravenous injection of mercuric chloride, the venous endothelium was only partially destroyed after twenty-four hours and completely destroyed after forty-eight hours. Endothelial destruction was incomplete until forty-eight hours and three days after the injection of mercuric chloride, 1 per cent., at which time it was estimated as 85 per cent. and 90 per cent., respectively. Hanschell[9] was unable to determine any change in the endothelium of a vein injected fifteen minutes previously with quinine hydrochloride, 13 per cent., sodium salicylate, 20 per cent.; and sodium chloride, 20 per cent. Veins which we examined immediately after the intravenous injection of sodium salicylate, 30 per cent., quinine and urea hydrochloride, and dextrose, 66 per cent., solutions had 90 per cent., 100 per cent. and 100 per cent., respectively, of the endothelium destroyed. (Chart II.) The apparent discrepancy between our results and those obtained by Hanschell[9] may be due to the fact that we employed more concentrated solutions, although the concentration of the quinine solutions were practically the same. A significant fact is that 71.2 per cent. of the observations made on or before the fourth day showed evidence of endothelial destruction, whereas only 16.7 per cent. of the observations made on or after the sixth day showed a similar destruction of the endothelium. This is undoubtedly due to the fact that between the fourth and sixth days a regeneration of the endothelium had occurred. This is in accord with the findings of Carrel and du Noüy,[15] Howes[16] and Harvey,[17] *et al.* Carrel and du Noüy[15] found that in the healing of wounds there was a latent period of from five to seven days before cicatrization occurred. Howes[16] and Harvey[17] found that in the healing of wounds in various tissues of the body there is a latent period of approximately four days before growth becomes appreciable. According to Regard,[11] defects in endothelium are rapidly replaced by a proliferation of the neighboring cells, and if proliferation is sufficiently rapid, the injured endothelium is covered with a "varnish" in order to prevent thrombosis. Binet and Verne[18] observed that a marked endothelial hypertrophy occurred following the intravenous injection of sclerosing substances, so that the endothelium resembled undifferentiated mesenchyme. Bazelis[7] found a marked proliferation of endothelium at the end of forty-eight hours, and Doerfell[19] was of the opinion that the endothelial proliferation is of great importance as regards the anchoring of the thrombus. Endothelial proliferation was found in 12.9 per cent. of the veins examined in the present investigation. There was no evidence of it within the first six hours. Four and four-tenths per cent. of the veins examined on or before the fourth day and 22.1 per cent. of those examined

on or after the sixth day had endothelial proliferation. As mentioned above, 71.2 per cent. of the veins examined on or before the fourth day and 16.7 per cent. of the veins examined on or after the sixth day had endothelial destruction. It is evident that the percentages of endothelial destruction and endothelial proliferation are inversely proportional to one another.

Other changes occurring in the endothelium of vessels following the intravenous injection of sclerosing substances have not been stressed by previous investigators. These are undoubtedly significant even though of less importance than destruction of the endothelial cells. As has been mentioned previously, in 18.9 per cent. of all the veins examined, a portion of the endothelial cells was destroyed so that the nuclei were exposed to the lumen of the vessel. This differed from complete destruction of the endothelium in that the nuclei and parts of the cells were still adherent to the wall of the vein. It is possible that eventually in these veins a complete destruction of the endothelium might have occurred. Fifty-six per cent. of the veins in which this phenomenon was observed were removed on or before the twelfth hour, whereas 44 per cent. were removed on or after the twenty-fourth hour. Thirty-seven per cent. of the veins extirpated on or before the fourth hour showed evidence of "exposure" of the nuclei, whereas only 11.6 per cent. of those made after the twenty-fourth hour showed this phenomenon. Another change which was observed in the endothelial cells was vacuolization, which occurred in 43.4 per cent. of the entire group of veins. This change occurred relatively early after the injection, as it was found in 53.8 per cent. of the veins examined on or before the tenth day and in only 25.2 per cent. made after this time. That these changes in the endothelium and in the other layers of the vessel wall and not only endothelial destruction are responsible for the development of thrombi, is evidenced by the fact that the degree of endothelial destruction is not always proportionate to the incidence of thromboses. This will be discussed more in detail under the question of thromboses.

An inflammatory reaction to the chemical trauma, consisting of œdema and leucocytic infiltration of the media and dilatation of the vasa vasorum of the adventitia was frequently found. The occurrence of œdema in the wall of vessels injected with sclerosing substances has been emphasized by Regard,[11] Meisen,[8] Schwartz and Ratschow,[20] and Lufkin and McPheeters.[21] In the present investigation, œdema occurred in 83.3 per cent. of the veins examined. (Chart III.) Ninety-eight and two-tenths per cent. of the observations made on or before the third week after the injection, and 16.1 per cent. of those made on or after the fourth week showed evidence of œdema. In the present investigation, there was no parallelism between the degree of œdema, the extent of endothelial destruction, and the number of thrombi. Leucocytic infiltration of the vein wall has been observed by Wolf,[14] Hanschell,[9] Howard and his collaborators,[10] Kern,[13] Schwartz and Ratschow,[20] Meisen,[8] and Lufkin and McPheeters.[21] Meisen[8] and Hanschell[9] found evidence of leucocytic infiltration twenty-four

hours after the injection. Kern[13] found that forty-eight hours after the injection of the sclerosing agent there was considerable inflammatory reaction which had completely disappeared at the end of a week. Schwartz and Ratschow[20] found that the inflammatory reaction had reached its height by the fourth day. Wolf[14] observed a marked leucocytic infiltration five to seven days after the injection and Howard, *et al.*,[10] stated that leucocytic infiltration was far advanced on the sixth day. In none of Lufkin's and McPheeters'[21] cases was there any evidence of abscess formation; the leucocytes were largely scattered throughout the muscle fibres of the media. In the present investigation, leucocytic infiltration occurred in 8.6 per cent. of all the veins. Five and two-tenths per cent. of all (63.4 per cent. of those with leucocytosis) occurred in veins removed twelve and twenty-four hours after the injection. Forty-five per cent. of the veins removed twelve and twenty-four hours after the injection showed evidence of leucocytic infiltration and of all the other veins examined before and after these two periods, in only 3.9 per cent. was there leucocytic infiltration. Fifty per cent. of the observations made at the end of twelve hours showed evidence of leucocytosis but there was no leucocytic infiltration after the third day. Possibly the apparent discrepancy between our findings and those of Wolf,[14] Howard, *et al.*,[10] as regards the duration of leucocytic reaction may be due to the fact that our observations were made on normal veins, the contents of which were in normal motion whereas the observations of the other investigators were made in patients' varicosed veins. Kern,[13] in his experimental animals, found that there was considerable inflammatory reaction after forty-eight hours but that it completely subsided within a week.

A phenomenon observed in the present investigation but one which has been scarcely mentioned in the literature is hæmorrhagic infiltration of the vessel wall. Meisen[8] mentions the occurrence of a perivascular hæmorrhagic œdema but does not refer to hæmorrhage in the vessel wall. Infiltration of the vessel wall with blood occurred in 2 per cent. of the veins examined in the present investigation. In 57.1 per cent. of the veins in which hæmorrhage was found, the injecting substance had been invert sugar either alone or combined with saccharose. No evidence of hæmorrhage was observed before the twelfth hour or after the fourteenth day. The greatest number occurred on the third day. Other evidences of inflammation found in the vessel wall were dilatation and an overfilling of the vasa vasorum, which occurred in 88.2 per cent. of all the veins examined. The highest incidence of the vasa vasorum dilatation was observed after the third hour and was most marked from then on up to the forty-eighth hour, although there was considerable dilatation of the vasa vasorum up to as long as eight weeks after the injection of the sclerosing agent. The finding of dilatation of the vasa vasorum has been emphasized by Meisen,[8] and Howard, *et al.*[10]

In addition to the destructive and inflammatory changes occurring in the vein wall following the intravenous injection of sclerosing substances, repara-

tive phenomena are also present. These changes consist of primarily the production of fibrous tissue and changes in the musculature of the media. An end-result which occurs in the wall of the vein as a result of the chemical trauma and the inflammation which has not sufficiently been stressed by previous investigators is fibrosis of the vessel wall. Kern[13] states that in his investigation he found the smooth muscle of the median coat of the vessel partially replaced by fibrous tissue. In the present investigation, fibrosis of the vessel wall, especially the media, but at times extending into the adventitia, was observed in 30.5 per cent. As might be expected, this was most marked in those observations made relatively late. Fifty-one and six-tenths per cent. of the observations made on or after the fourteenth day showed evidence of connective-tissue proliferation. It is probable that the fibrosis of the vessel wall is important as regards the ultimate results obtained by the injection treatment of varicosities in that contraction of the fibrous tissue tends to diminish the size of the lumen and strengthen the vessel wall. This is especially important in view of the fact that recanalization of the thrombus is especially likely to occur.

A phenomenon which we cannot find described by previous investigators but which was consistently found in a large number of the veins studied in this particular investigation is the reaction of the smooth muscle cells to the chemical trauma. This reaction consisted largely of a hypertrophy of the cells of the media as evidenced by an increase in their size. In 70.7 per cent. of the observations made there was evidence of muscle hypertrophy. It is possible that in some of the veins examined soon after the injection of the sclerosing agent the increase in the size of the muscle fibres which was interpreted as hypertrophy was in part due to an œdema, as œdema was found to be present in all the veins examined on or before the fourth day. Seventy-nine and five-tenths per cent. of the veins extirpated on or after the sixth hour showed evidence of muscle hypertrophy. In a relatively large number of instances, there was a suggestion of muscle hyperplasia, which was thought to be present because of apparent invasion of the adventitia by the smooth muscle cells and bundles of the media. It is commonly thought that regeneration of smooth muscle cells does not occur. According to Marchand,[22] healing of an artery occurs by cicatrization without the individual elements of the vessels, especially the smooth musculature, taking part in the regeneration. Razzaboni[23] found that the regeneration of muscle in the vessel wall seldom occurs and then only to a slight degree. That newly formed smooth muscle cells can occur is shown by the investigation of Berry,[24] who was able to demonstrate that following injury to the human, guinea-pig and rabbit uteri, there occurred an increase in the number (hyperplasia) of smooth muscle cells. The authors agree with Berry[24] that, in wounds of smooth muscle, healing occurs largely by cicatrization but that even though the defect in the vessel may be largely closed by the production of scar tissue, in addition there occurs in the region of the wound an actual increase in the number of smooth muscle fibres. This contention is substantiated by the findings in the present investigation, although in no instance

was there evidence of mitosis observed in the smooth muscle cells. Maximow and Bloom[25] state: "Completely developed smooth muscle cells in the adult organism keep the ability to divide by mitosis to a certain degree—but this capacity for regeneration is small and as a rule great defects in smooth muscle tissue heal by scar formation. Whether smooth muscle cells in the adult organism may be formed from fibroblasts has not been established. It is practically certain that they may develop from the perivascular embryonic cells of the adult." The explanation for the muscle hypertrophy and the attempt at hyperplasia is probably that as a result of weakening of the vessel wall by the inflammatory reaction, an attempt is made on the part of the musculature to compensate for this by hypertrophy and possibly hyperplasia.

In the injection treatment of varicose veins, the desired result is obliteration of the vessel. This may be accomplished either through the medium of a thrombus or by producing agglutination of the two injured endothelial surfaces following their apposition. In the present investigation, no attempt was made to compress the vessels so that obliteration was secured only by the production of thrombi. Most of the previous investigators, Meisen,[8] Wolf,[14] Schwartz,[12] Hanschell,[9] Howard, *et al.*,[10] found that fibrinous thrombi occur within twenty-four hours after injection. Kern and Angle[26] did not make observations until after forty-eight hours, but then found fibrinous thrombi. Bazelis[7] found no thrombi at the end of twenty-four and forty-eight hours following the intravenous administration of mercuric iodide, but observed fibrinous thrombi at the end of seventy-two hours. In the present investigation fibrinous thrombi occurred in 8.9 per cent. of all the veins examined. We were unable to corroborate Bazelis'[7] observations as 30 per cent. of the veins examined by us one-half hour after the injection contained fibrinous thrombi. Fifty-one and six-tenths per cent. of all the veins with fibrinous thrombi were extirpated between the second and fourth days, inclusive, after the injection. The highest incidence of thrombi occurred in veins removed forty-eight hours after the injection. Of 121 observations made on or before the twenty-fourth hour, fibrinous thrombi occurred in 10 per cent., whereas of the twenty veins removed forty-eight hours after the injection fibrinous thrombi occurred in 35 per cent. Those substances which caused the greatest number of fibrinous thrombi were sodium salicylate, 40 per cent., and mercuric chloride, 1 per cent.

Only about one-half as many fibrous thrombi (4.59 per cent.) as fibrinous thrombi were observed. All occurred in veins removed fourteen days or longer after the injection. Sixty-eight per cent. of the organized thrombi occurred in veins removed between the second and fourth weeks. The largest number of fibrous thrombi was caused by sodium salicylate, 40 per cent.; quinine and urea hydrochloride; sodium salicylate, 30 per cent., and sodium chloride, 10 per cent. A relatively small number (13.2 per cent.) of thromboses occurred in the veins examined in the present investigation, as compared with those which occur in the varicose veins of patients injected with sclerosing agents. This is in all probability due to the fact that the veins

injected in the present series were normal, and that no stasis was present, which, as Aschoff[1] has shown, predisposes to thrombosis. The present results indicate that even extensive destruction of the endothelium need not be associated with thrombosis in the normal vein, although Aschoff states, "when, instead of slow retrogressive changes, the intima is suddenly stripped of its endothelial lining, then a reaction inevitably ensues, as occurs in all living tissues, accompanied by a pathological flow of lymph. Then it is indeed the alteration in the blood-stream in the region of the injured area which brings about a thrombosis by deposition."

The marked endothelial regeneration is probably partially responsible for the small number of thrombi. That thrombosis did not occur within the first four days after the injection before endothelial regeneration became marked may be due to a "varnishing" of the destroyed endothelium, as has been described by Regard.[11]

All except one (94.4 per cent.) of the fibrous thrombi showed extensive evidence of recanalization. Canalization of the thrombus occurred most frequently in the veins injected with sodium salicylate, 40 per cent.; sodium salicylate, 30 per cent. and sodium chloride, 10 per cent.; mercuric chloride, 1 per cent.; and quinine and urea hydrochloride solutions. There was no evidence of recanalization on or before the tenth day, whereas all evidence of canalization occurred on or after the fourteenth day. Recanalization of the thrombosed vein may be responsible for the high incidence of recurrences reported by Howard, *et al.*[10]

As mentioned above and as has been previously stressed by deTakats and Quaint,[27] Kern,[13] and Ochsner,[28] obliteration of a varicose vein may be secured with a minimum amount of thrombosis, by approximating (localized pressure over the injection portion) the injured endothelial surfaces and thus securing agglutination of the approximated surfaces. That venous occlusion secured in this way is preferable to that produced by a large thrombus is obvious, for the following reasons: First, a large thrombus becomes recanalized and may result in a recurrence. Second, any thrombus is a potential embolus. Both of these objections are more apparent than real, however. Even though recanalization does occur, the fibrosis in the vein wall tends to prevent subsequent venous dilatation. Then, too, not in all cases in which there is a return of symptoms is there a true recurrence, because in many there is involvement of other previously uninvolved veins.

As is shown by the firm anchoring of the thrombus to the vessel wall by its invasion by fibroblasts from the wall of the vein, there is little danger of a detachment. The inflammatory reaction which occurs infrequently (8.6 per cent. of cases) is almost entirely confined to the media and is of such a character that liquefaction of the thrombus as the result of the digestive action of tryptic ferments derived from leucocytes is not apt to occur.

Aside from the interesting and possibly valuable observations made concerning the effect of various sclerosing substances on the wall of veins, the present investigation is also probably of some value as regards the practical application of this form of therapy in the clinic. The desired result in the

treatment of varicose veins is obliteration of the varicosity by some means. Preferably, for reasons given above, this may be accomplished by compressing the vein and thus causing agglutination of the injured endothelial surfaces. Obliteration of the vein may also be accomplished by the production of a thrombus, which will subsequently become organized. In the present investigation following the intravenous injection of sclerosing agents, no attempt was made to determine what effect compression would have on the vein; the comparative results produced by the intravenous injection of various sclerosing substances must, therefore, be based upon the number of thrombi which developed. As shown in Table III, sodium salicylate, 40 per cent., produced the greatest number of thrombi (fibrinous and organized) as well as the most extensive endothelial destruction. It is thus evident that of the various sclerosing substances investigated, sodium salicylate, 40 per cent., is the most efficacious as regards the production of thrombi and probably would be the most efficacious in obliterating the vein if the vein were collapsed, because of its highest incidence of endothelial destruction. It is logical to assume that following destruction of the endothelium, approximation of the endothelial surfaces is apt to result in an agglutination of the two surfaces. From a practical standpoint, however, sodium salicylate, 40 per cent., has many objections in its clinical use, the principal ones being the severe cramp which it produces and the marked slough which occurs if a perivenous injection is made. Solutions of sodium salicylate, 30 per cent., and sodium chloride, 10 per cent., were also efficacious in producing organized thrombi, even though the number of combined thrombi and the amount of endothelial destruction were not great. The same objections to the clinical use of this solution may be offered as for sodium salicylate, 40 per cent. The next most efficacious agent in producing organized thrombi was mercuric chloride, 1 per cent., which also was the most efficacious agent in producing connective-tissue proliferation of the media. That mercuric chloride should not be used as a sclerosing agent is exemplified by the fatalities from mercurial poison which has resulted from the intravenous injection of this substance. Such cases have been reported by Hammer[29] and Mundt.[30] Quinine and urea hydrochloride solution was fourth in efficacy in producing organized thrombi and second in destructive action on the endothelium. Clinically, quinine and urea hydrochloride solution has many advantages. It can and should be used in small quantities and produces little or no pain. Also the danger of the development of necrosis if perivenous injection is made is much less than that obtained with the above-mentioned agents. Its use, however, is contra-indicated in patients with an idiosyncrasy to quinine and during pregnancy and menstruation. A solution of invert sugar, 75 per cent., and saccharose, 5 per cent., was fifth in efficiency in producing organized thrombi, whereas the next most efficient agent as regards development of organized thrombi was invert sugar, 75 per cent. The sugar solutions clinically have many advantages over the hypertonic salt solutions in that their injection is relatively painless. Invert sugar solutions, also, because of their lessened viscosity as compared with dextrose solutions, can be

injected relatively easily. The reaction which is produced is not so severe as that produced by the concentrated salicylate solutions and the danger of slough occurring if a perivenous injection is accidentally made is relatively slight. Sodium chloride, 25 per cent., followed invertose, 75 per cent., as regards the ability to produce organized thrombi. Sodium chloride solutions are, however, extremely irritating to the vein and their intravenous injection is extremely painful.

If one were justified in drawing conclusions from the results obtained in the present investigation which might be applicable to the treatment of patients with varicose veins, it seems permissible to suggest that because of the relatively high efficiency of the sugar solutions, especially invert sugar, 75 per cent., and invert sugar, 75 per cent. and saccharose, 5 per cent., in producing organized thrombi in normal veins of animals and because of the relatively few untoward symptoms which intravenous injection of these substances produces, these should be used in the routine treatment of patients with varicosities. If, however, the vein were small and there were no contra-indications to the use of quinine, quinine and urea hydrochloride would probably be more efficacious. In those instances in which one failed to obtain obliteration of the vein following the injection of the sugar solutions and quinine and urea hydrochloride, one would be justified in using the stronger concentration of salicylate solutions, especially sodium salicylate, 40 per cent. That this substance could not be used routinely is evident, because of the severe and painful reactions which it produces.

Additional investigations are being made, especially with the newer sclerosing agents that have been suggested.

SUMMARY AND CONCLUSIONS

(1) A comparative study of the effects of twenty different sclerosing substances on the veins of the dog is presented. In all, 348 histological examinations are made, extending from one-half hour to eight weeks after the injection.

(2) The changes in the vein wall consist of destructive, inflammatory and reparative changes.

(3) Endothelial destruction was observed in 45.1 per cent. of the veins. It was greatest in the veins examined on or before the fourth day. Regeneration of the endothelium occurred in a large number of instances between the fourth and sixth days. Other destructive changes in the endothelium were vacuolization and partial destruction of the endothelial cell.

(4) The inflammatory reaction consisted of œdema (83.7 per cent.), leucocytic infiltration (8.6 per cent.) and dilatation of the vasa vasorum (88.2 per cent.).

(5) The reparative changes consist of muscle hypertrophy (70.7 per cent.), fibrosis of the vessel wall (50.5 per cent.).

(6) Thrombi occurred in only 13.2 per cent. of all veins; of these, 67.4 per cent. were fibrinous and 34.8 per cent. were fibrous. Canalization of fibrous thrombi occurred in 94.4 per cent.

(7) Sodium salicylate, 40 per cent., produced greatest injury to the vein wall and the largest number of thrombi. Combining the results obtained in this investigation with clinical experience, it is felt that of the group of agents studied, invertose, 75 per cent., or invertose, 75 per cent. combined with saccharose, 5 per cent., should be used for routine clinical use. If these fail, quinine and urea hydrochloride and the higher concentration of sodium salicylate (40 per cent.) should be used.

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Discussion.—Dr. John Homans (Boston) brought up the question as to whether or not a varicose vein is likely to be a source of thrombosis, as compared with one hitherto normal. Apparently embolism from varicose veins is rare, the reason being because their walls are diseased and the thrombus is more adherent than in normal veins. In any case, it seems to be true that the number of cases of embolism from thrombosis in hitherto normal veins is greater, at least relatively greater, than from varicose veins.

Is it not advisable to do more ligations of the femoral in Hunter's canal for local thrombophlebitis in the lower leg?

He recalled three cases of this disease. One died of embolism following an illness of several weeks. Another followed too violent massage; the patient was ill for a long time and finally recovered. The third case had frequent recurrences and seemed to be in danger of embolism, so Doctor Homans tied the femoral vein in Hunter's canal, for it seemed to him there was no way a clot could arrive at the lungs from the deep vessels of the calf except by way of the femoral veins. For in the veins communicating with those of the surface the current is from without inwards, the veins in any case are small, and so, if one ties the femoral vein, there will be no embolism. In the case treated by ligation recovery was rapid and satisfactory.

That brings up the question of whether the ligation itself may not be a source of trouble. He was quite sure that thrombosis in veins, whether normal or pathological, will almost always progress toward the heart until a strong current is reached, so that if one is to ligate a vessel to prevent the extension of clot, on the whole it is better to ligate near an entering branch. Doctor Matas had suggested that in connection with the ligation of arteries, but it is also true of the veins. One should ligate near but not too near an entering branch. He brought up this question, which is rather a fussy one, perhaps, as to where the ligation should be performed, because it may be true in some of these cases that the thrombosis is due to a factor, in any particular patient, of which we know nothing, and the thrombosis is likely to continue unless one takes pains to so conduct the operation that it will be the least likely to continue.

Dr. Howard Lilienthal (New York City) remarked that he had for a long time been advising that in the cases of œsophageal injury with or without perforation, particularly on the right side, when the patient has fever and other signs of sepsis, especially when the blood gives a positive culture, the major axygos vein should be ligated and cut through a posterior mediastinotomy. One instance seen by him, a woman about thirty years old, had swallowed a fish bone. The characteristic signs of sepsis were present but this operation was refused.

One may find a view of the exposure as he has made it, as the colored frontispiece, in a book that he wrote in 1925 (Thoracic Surgery, W. B. Saunders).

Dr. Fred B. Lund (Boston) had operated upon no thromboses of femoral veins, but in varicose veins he had seized upon the thromboses as the most favorable condition for ligating the saphenous and removing the varicosities. In the first place, the more extensive the thromboses, the more good one does. They are red and sore and will take weeks and weeks to absorb. Tie the vein above and remove them, without the usual bleeding that takes place when they are not thrombosed. It is not a major operation.

In the injection treatment of varicose veins one is trying to make a local clot. Here the patient is in bed with a large clot all the way down the leg. If it is stripped out, weeks and weeks of time are saved for him.

Dr. Arnold Schwyzer (St. Paul) said that one had only heard now of ligating those veins in cases of sepsis, but when, especially in a saphenous vein, the process has reached far up, that is a dangerous procedure because we do not know whether we are ligating too near the infectious part or maybe even below the infectious process (floating thrombus).

He remembered his first case of this kind, forty years ago. He was called to see a woman suffering from puerperal sepsis. She was six weeks after childbirth, with high temperature, both legs swollen, and redness over several areas of the right saphenous. Fifteen incisions were made, only incisions, to let the partly broken-down thrombi come out. The incisions were made all along the leg, as far as the very origin of the saphenous vein, but he didn't squeeze the parts to any extent. There was no bleeding, but if there should be bleeding here or there, so much the better.

In another case of puerperal sepsis things looked as though the woman was going to die; the temperature rose to 105°. They removed the septic uterus, but found on the right side a very thick cord running up toward the kidney region. They went extraperitoneally into this cord formed by the thrombosed ovarian vein, tore the infiltrated areolar tissue apart, opened the vein, and thus gave an outlet for the pus. The woman got well.

If the incision is away from the septic process, then the ligation, even quite a distance away, may be excellent. In one case of an apparently cryptogenetic sepsis, a man had temperatures of over 106° with daily chills of the most formidable type. They could not find anything except an uncertain little tenderness of the right side of the prostate. They finally went in and ligated the internal iliac vein, and the chills stopped. A week after this operation the chills reappeared. However, in the meantime, about a week after the operation, they could feel a slight bulging per rectum. Going in from the perineum some pus was found, and the patient got well without the left-sided ligation.

So, when one has a septic condition to deal with, azygos or saphenous or other, all one may have to do when one reaches the site of thrombosis is cut into the thrombosed vein for drainage.

Dr. Rudolph Matas (New Orleans) agreed thoroughly in principle with Doctor Stone's attitude in ligating and extirpating thrombosed inflamed veins whenever this was practicable. This is the best practice in hastening recovery and preventing secondary embolism. Unfortunately, this practice has decided limitations. One would not hesitate in dealing with the saphenous or the superficial veins but would hesitate and must halt when facing the femoral, iliac and other deep veins. Here the difficulty lies in determining the limit of the thrombophlebitic invasion. By the time the diagnosis is clearly established, one may be sure that the thrombus has extended into the iliac tracts far above the groin. Logically, the principle of preventive ligation and division of the iliac veins is even more indicated than in the superficial saphenous, for there the danger of fatal pulmonary embolism is much greater. The preventive ligation of the external

and internal iliacs and even the vena cava, as this has been carried out in a number of cases of progressive post-operative thrombosis and puerperal pelvic phlebitis, has not yielded encouraging results. Apart from the gravity of the intervention in the conditions under which it is performed, the uncertainty of reaching the limit of the thrombophlebitic process has deterred surgeons from adopting preventive ligations and excisions in the deep veins as a regular procedure.

Doctor Stone has done well to caution against overconfidence in the reputed benignity of the superficial saphenous thromboses. These are usually regarded as comparatively free from the risk of pulmonary embolism. While this is true of the majority of the cases there are too many exceptions to permit one to disregard the embolic risk.

In connection with Doctors Ochsner's and Garside's paper, he had recently had to lament a fatality from pulmonary embolism caused by the injection of less than one cubic centimetre of quinine urethane into a varix of the internal saphenous. The patient was a healthy, robust man of forty years and the varix stood out as a superficial coil which did not involve more than five inches of the vein. The injection had no immediate notable consequence, but within a week the patient developed an acute (afebrile) thrombophlebitis of the deep femoral veins with pain and great œdema of the whole limb. The injection evidently started a phlebitis which rapidly extended from the superficial to the deep veins by the communicating branches. The swelling was subsiding and the patient improving in general, when, at the end of the third week after he had developed the phlebitis, he died suddenly in a paroxysm of dyspnœa and precordial distress. He was reading a newspaper calmly when the embolus came and in little over a minute he was dead.

This is about the thirtieth embolic fatality following sclerosing injections for varicose veins that have been recorded in the literature. He was confident that the list could be much increased if the unreported cases were added.

Embolism and infarction may be regarded as exceptional occurrences when the number of the recorded fatalities is pitted against the hundreds of thousands of cases that are being injected all over the world with seeming impunity. But a single tragedy such as he related is sufficient to make one wary of all statements which proclaim the innocence and safety of the sclerosing intravenous injections.

Doctor Beer, in his admirable study of the azygos system, has opened a new chapter in regional phlebopathology and unveiled one of the most hidden recesses and least-frequented paths of the venous circulation in so far as the diagnostician and clinical pathologist are concerned.

In connection with the symptomatology of the azygos vein, Doctor Matas directed attention to a sign which is frequently observed in the physical examination of the chest and which he had interpreted as evidence of stasis or prolonged strain of the azygos system. This sign usually presents itself as a capillary venous ectasis in the form of a fine delicate network of dilated vessels which somewhat resemble a nevus araneus or a caput medusæ on a fine scale, spread as a narrow strip along the skin of the intercostal spaces on both sides of the chest. It appears usually along the line of the sixth, seventh, or eighth interspaces. The appearance of this network suggests that it is constituted by cutaneous radicals of the intercostal veins which become visible only when there is a persistent strain or obstructive stasis of the azygos or superior caval veins.

They appear in adults or individuals past middle age, more often in athletic individuals and working people who carry heavy burdens. Clinically, they always suggest some intrathoracic cause of interference with the upper caval and azygos circulation. These capillary ectases are so fine that they usually escape the observation of the patients themselves. These capillary networks must not be confused with the larger dilated varicose veins which develop as a compensatory collateral circulation in cases of permanent caval and portal obstructions. Their close relation to the diaphragmatic attachments has suggested the name "Corona Phrenica" by which it is known in his clinic.

THE DIFFERENTIATION OF SPASTIC FROM ORGANIC PERIPHERAL VASCULAR OCCLUSION BY THE SKIN-TEMPERATURE RESPONSE TO HIGH ENVIRONMENTAL TEMPERATURE

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Many studies carried on in recent years on peripheral vascular diseases have clarified the classification of these lesions and emphasized the importance of recognizing the type of vascular occlusion present. The recognition of the value of skin-temperature measurements has played an important part in furthering these studies.

One of the major functions of the skin is the dissipation of body heat. The temperature of the skin is a resultant of the heat brought to it by its blood supply and the loss of heat from its surface by radiation, conduction, convection and the vaporization of water. In normal subjects at light activity approximately 24 per cent. of the total heat dissipated is by the vaporization of water from the skin and lungs. External heat and cold modify the amount of blood supplied to the skin and thereby vary the skin temperature. This response of the organism to the environment is called the physical regulation of body temperature.[1]

During the past two years we have studied the response of the skin temperature to changes in environmental temperature in normal individuals and in patients with peripheral vascular disease. The observations of the normal persons are recorded in Part I and those of patients with peripheral vascular disease in Part II.

PART I: NORMAL SUBJECTS

Procedure.—The study was carried on in a small room in which the temperature was kept fairly constant. A circulation of air was maintained by a small electric fan running at low speed. The points of skin temperature measurement were chosen with particular attention to the extremities and are shown in Fig. 1 with their identifying numbers. A "Tycos Dermatherm"[2] was used for all skin-temperature measurements. Thirty normal individuals between the ages of thirteen and sixty years were studied in order to establish the normal response. The subject, lying quietly on a stretcher and covered only with a perineal drape in the case of the men, and a perineal drape and a towel over the breasts in the case of the women, was exposed to the environmental conditions for one hour.* The skin temperatures at the various body points were recorded. The subject was then covered with a light rubber sheet† to the clavicular

* The one-hour period was selected because in that time the skin temperature reaches a reliable constancy of adjustment to a constant environmental condition.

† The rubber sheet was added to the blankets in order to better hold body heat and to raise more quickly the private environmental temperature. Air temperature beneath these coverings was found to range from 34.0° C. to 38.0° C.

line and wrapped up in three woolen blankets. (Fig. 2.) At the end of one hour skin-temperature measurements were again taken. The coverings were moved only sufficiently to apply the applicator to the skin so that the readings obtained would be as nearly as possible the skin temperatures as they existed under the coverings.

Data.—The response obtained from a representative group of six of the normal men and women is presented in Tables I and II. Columns A show the skin temperatures for the exposed period, columns B for the covered period. The averages of the skin temperatures at the various body points are plotted as curves on Chart 1.

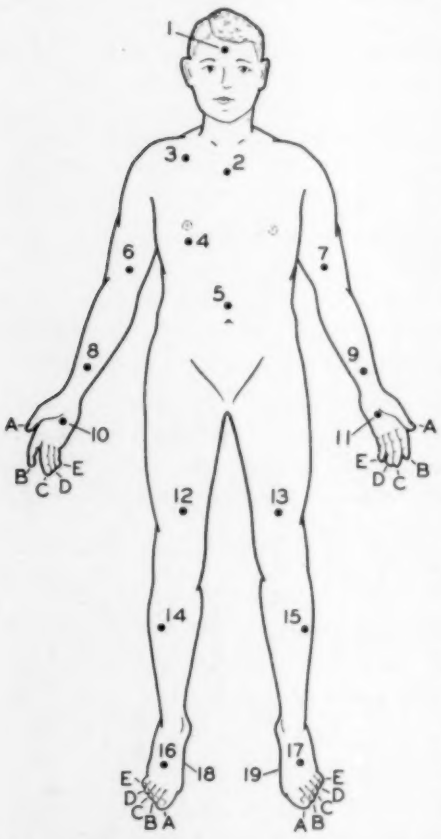


FIG. 1.—Points of skin-temperature measurement.

From an examination of the data for the exposed period, the following facts were elicited:

(1) The highest skin temperatures prevailed on the trunk, the lowest at the tips of the extremities, with greater differences occurring at lower environmental temperatures.

(2) A progressive lowering of the skin temperature of the extremities occurred from the proximal to the distal points measured. This gradient was more marked in the lower than in the upper extremities. In general, there was also a slight progressive lowering of the skin temperature from the tip of the first to the fifth digits.

(3) In many instances under comparatively similar environmental conditions there was a fairly close approximation of the skin temperature of the same body point on different individuals. This fact is demonstrated by comparing subjects G. J. with E. S., A. B. with I. J., V. C. with E. G.

(4) Under essentially similar environmental conditions, differences occurring in the skin temperature of the same body point on different individuals were greater towards the tips of the extremities, and were more marked in the toes than in the fingers. Examples in comparing subjects J. G. with J. B., V. C. with E. G.

(5) Under similar environmental conditions the trunk points on men and women were approximately the same, while lower temperatures prevailed on the extremities of women than men. Example in comparing subject G. L. with A. K.

(6) No constant figure was found as a correction factor to correlate the differences in the skin temperature of individuals to different environmental temperatures.

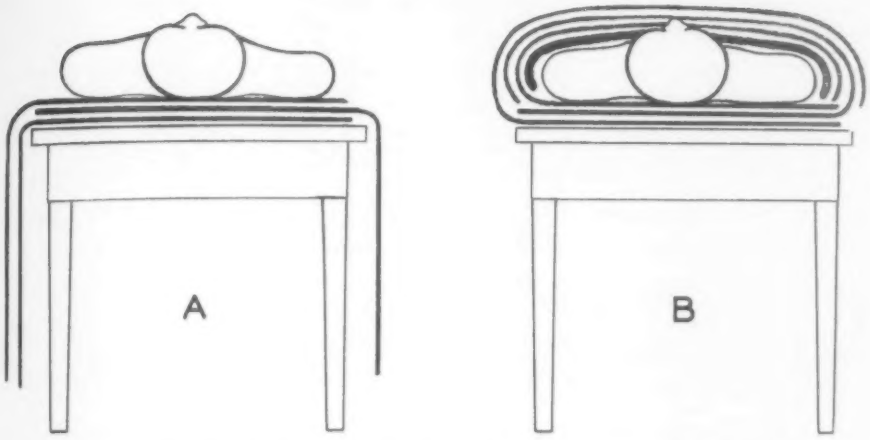


FIG. 2. (A)—Arrangement of blankets for exposure period. (B)—Arrangement of rubber sheet and blankets for covered period.

TABLE I

Data from Study of Six Normal Men

	MEN																	
SUBJECT, AGE.	J.G. 60		G.J. 33		C.L. 41		J.B. 15		N.M. 19		E.S. 18		AVERAGE					
DATE	3-24-31		3-22-31		3-4-31		4-15-31		4-9-31		4-9-31							
COLUMNS	A	B	A	B	A	B	A	B	A	B	A	B	A	B				
TIME	10:50	11:50	10:00	11:00	8:50	9:50	10:25	11:25	3:20	4:20	10:25	11:25						
ROOM TEMP. °C	24.0	24.0	25.5	24.0	24.0	24.0	24.5	24.0	27.0	27.5	25.5	26.0	25.0	24.9				
MOUTH TEMP. °C	37.0	37.1	36.9	37.0	36.7	36.8	36.8	36.8	37.0	37.0	37.0	37.0						
BODY POINTS																		
1	30.4	33.2	32.7	30.1	31.6	31.3	31.2	31.1	32.8	32.6	32.5	31.5	31.8	31.6				
2	30.3	33.9	32.8	32.2	32.4	33.6	30.5	32.9	32.6	32.3	32.5	33.3	31.8	31.6				
3	30.0	34.4	32.5	32.3	32.5	33.6	30.8	33.1	32.8	31.8	32.4	33.3	31.9	33.2				
4	30.8	34.3	33.7	32.6	33.0	34.9	29.9	33.5	32.9	33.2	32.7	33.3	32.2	33.1				
5	30.5	35.2	33.5	35.4	33.0	34.2	29.0	34.4	33.9	34.3	34.1	34.8	32.3	33.6				
6	30.3	34.5	32.9	34.3	32.2	34.1	29.9	33.6	32.9	33.3	32.5	33.5	31.8	34.7				
8	30.9	34.6	32.5	34.8	30.9	34.1	30.6	33.7	33.1	33.3	32.4	33.8	31.7	33.9				
10	30.6	34.2	31.9	34.7	31.7	34.0	29.1	33.9	33.1	33.8	32.7	33.7	31.5	34.0				
" a	29.5	34.4	31.5	34.9	31.8	34.2	29.6	33.0	33.1	33.5	32.2	32.8	31.3	34.0				
" b	29.6	34.4	31.5	35.1	31.8	34.4	30.3	33.8	33.1	33.5	32.7	33.7	31.5	33.8				
" c	29.8	34.8	31.5	35.1	31.5	34.5	30.7	33.8	32.9	33.5	32.0	33.5	31.4	34.1				
" d	29.4	35.0	31.5	35.0	31.6	34.7	30.5	34.0	33.4	33.6	32.0	33.8	31.4	34.2				
" e	28.9	35.3	30.1	35.2	31.4	34.6	30.3	33.0	32.5	33.6	31.9	34.1	30.8	34.3				
7	31.5	35.3	33.5	35.0	32.5	33.8	30.2	33.8	33.1	33.8	33.2	34.3	32.3	34.3				
9	31.0	35.5	33.2	35.5	32.0	34.3	29.4	33.9	33.8	34.1	33.2	34.5	32.1	34.6				
11	31.4	35.6	32.6	35.7	32.4	34.2	29.0	34.2	33.4	34.6	33.4	34.8	32.0	34.9				
" a	30.0	35.5	32.1	35.7	31.5	34.5	30.0	33.2	33.1	34.3	32.5	33.9	31.5	34.6				
" b	29.9	35.3	32.0	35.8	32.4	34.7	29.6	33.4	32.8	33.6	32.5	34.1	31.5	34.5				
" c	29.9	35.5	31.9	35.8	32.2	34.9	30.3	33.6	32.3	33.6	32.5	34.3	31.5	34.6				
" d	29.4	35.6	31.7	35.8	31.6	34.8	30.3	34.4	32.3	33.8	32.5	34.3	31.3	34.8				
" e	29.2	35.7	31.5	35.8	31.6	34.8	31.0	33.7	32.5	33.3	32.4	34.6	31.4	34.7				
12	30.3	34.7	33.2	35.7	33.2	34.7	28.7	33.7	34.1	34.8	33.5	34.3	32.2	34.6				
14	29.6	34.3	32.1	35.9	31.5	34.2	31.0	33.5	32.9	33.3	33.3	34.3	31.7	34.7				
16	30.2	34.3	30.5	35.5	30.5	34.2	29.2	33.7	32.9	33.8	34.1	34.5	31.2	34.3				
18	28.3	35.2	29.9	34.8	28.9	34.3	28.2	34.5	31.1	34.3	31.3	34.3	29.6	34.6				
" a	26.6	35.4	29.5	34.7	25.8	34.4	28.2	33.4	31.9	33.6	28.2	34.3	28.4	34.3				
" b	27.5	35.4	27.5	34.9	25.1	34.5	24.6	33.7	31.5	33.6	31.2	34.3	27.9	34.4				
" c	27.0	35.4	27.7	35.2	24.5	34.5	24.8	33.7	30.6	34.1	27.5	34.5	27.0	34.6				
" d	26.9	35.4	28.0	35.4	24.4	34.5	25.1	33.2	31.1	33.6	27.1	34.8	27.1	34.5				
" e	26.9	35.4	28.5	35.3	25.0	34.5	25.9	33.4	30.9	32.8	27.2	34.5	27.4	34.3				
13	30.2	34.6	30.5	35.8	32.2	34.5	29.0	34.4	33.8	34.3	32.9	34.6	31.5	34.7				
15	30.0	34.3	32.0	35.1	30.8	34.4	27.3	34.1	33.2	34.3	34.1	35.1	31.2	34.9				
17	29.7	34.8	30.5	35.2	29.4	34.9	29.3	34.1	32.4	34.3	32.4	35.3	30.6	34.8				
19	29.0	34.4	29.7	34.1	28.9	34.5	28.0	35.2	31.3	33.8	31.2	35.2	29.7	34.6				
" a	28.6	34.8	30.1	34.8	25.4	34.7	25.5	34.6	31.3	33.6	27.1	34.6	28.0	34.6				
" b	27.8	35.0	29.5	34.8	25.2	34.9	24.0	34.1	30.7	33.3	26.5	34.6	27.3	34.5				
" c	27.8	35.2	29.5	34.6	24.3	34.9	26.9	34.1	30.7	33.8	28.1	35.5	27.9	34.7				
" d	27.6	35.0	29.5	34.6	25.0	34.9	25.8	34.0	30.7	33.3	28.2	35.3	27.8	34.6				
" e	27.9	35.2	29.5	34.8	24.7	34.9	25.1	33.2	30.9	33.3	27.9	34.9	27.7	34.4				

Comment.—We will confine this discussion to the facts pertinent to the points we wish to emphasize in this paper. Benedict, Miles and Johnson, in 1919,[3] demonstrated that on exposure of the body to moderate temperatures there prevailed higher skin temperatures on the trunk than on the extremities. Morton and Scott[4, 5] consider this phenomenon to be due to vasoconstriction increasing peripherally and have applied to it the term

TABLE II

Data from Study of Six Normal Women

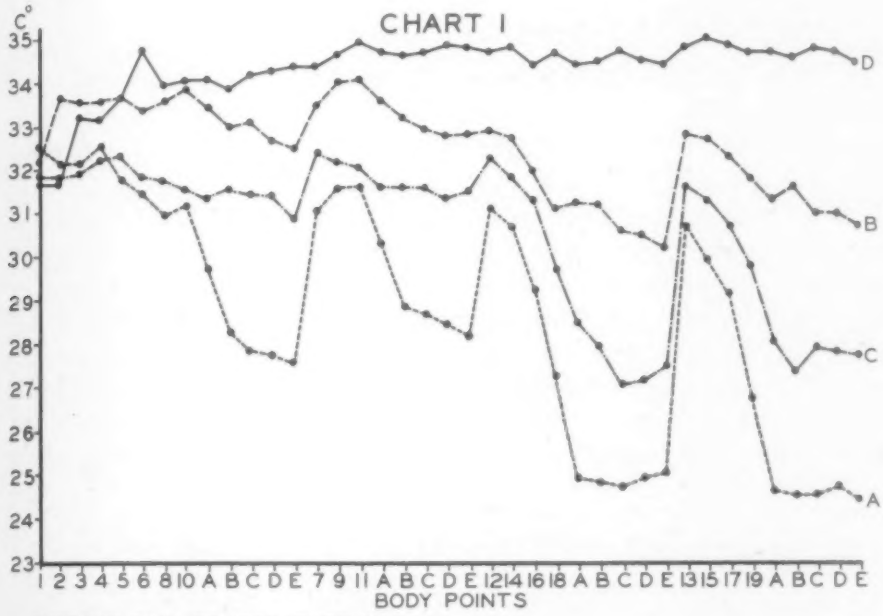
	WOMEN														AVERAGE	
SUBJECT, AGE.	A.B. 23		I.J. 50		M.G. 38		A.K. 21		V.C. 17		E.G. 23					
DATE	9-25-31		9-28-31		11-30-31		11-30-31		12-1-31		12-1-31					
COLUMNS	A	B	A	B	A	B	A	B	A	B	A	B			A	B
TIME	11:00	12:00	3:20	4:20	9:45	10:45	9:50	10:50	10:50	11:50	10:55	11:55				
ROOM TEMP. °C.	23.0	24.0	23.0	23.0	24.6	24.0	24.6	24.0	27.0	27.1	27.0	27.0			24.8	24.9
MOUTH TEMP. °C.	37.0	37.0	36.9	37.0	37.1	37.0	37.3	37.0	37.1	37.4	37.2	37.5				
BODY POINTS																
1	32.1	32.4	32.1	33.7	31.6	30.8	33.0	32.6	32.4	31.2	33.3	32.9			32.4	32.3
2	32.0	33.5	32.1	34.3	31.1	32.1	32.7	33.8	32.4	32.4	32.3	34.4			32.1	33.6
3	31.9	32.0	32.2	34.3	30.6	31.9	32.6	33.9	32.2	33.5	32.6	34.5			32.0	33.5
4	32.0	33.3	32.6	33.9	31.7	32.0	33.0	34.0	33.0	33.5	32.5	34.2			32.5	33.5
5	31.1	32.7	32.1	34.1	30.1	31.8	32.1	34.0	31.8	33.5	32.9	34.9			31.7	33.5
6	32.2	32.2	32.2	34.0	29.9	31.7	31.4	33.8	30.4	33.1	32.2	33.8			31.4	33.3
8	30.1	33.3	30.2	34.2	30.5	32.1	31.1	33.6	31.7	32.5	31.7	34.1			30.9	33.5
10	29.2	33.5	30.3	34.1	29.7	32.9	31.7	34.4	32.9	33.6	33.6	34.9			31.1	33.9
" a	26.5	33.1	28.8	33.7	28.0	32.6	30.6	33.7	32.0	32.7	32.1	34.2			29.7	33.3
" b	26.5	33.0	27.0	33.4	25.2	32.2	28.2	33.0	31.5	32.5	31.0	33.6			28.2	32.9
" c	26.2	33.0	26.0	33.2	24.3	32.0	27.6	33.4	31.7	32.5	30.8	34.0			27.8	33.0
" d	26.1	32.7	26.0	33.1	23.6	31.7	28.8	32.5	31.7	32.3	30.3	33.4			27.7	32.6
" e	25.5	32.3	25.5	33.0	23.2	31.5	29.1	32.4	31.9	32.2	30.1	33.0			27.5	32.4
7	30.5	33.5	31.7	33.7	29.6	31.9	31.2	33.6	31.7	33.6	31.2	34.0			31.0	33.4
9	29.8	33.6	31.7	34.3	31.8	32.6	31.2	34.4	31.8	33.8	33.0	34.8			31.5	33.9
11	28.8	33.3	30.8	33.9	31.2	33.4	30.6	34.7	33.8	33.5	34.1	35.3			31.5	34.0
" a	26.0	32.9	28.0	33.7	27.7	33.1	30.1	33.2	32.8	33.4	32.3	34.5			29.5	33.5
" b	26.4	32.7	26.7	33.5	25.0	32.0	30.1	32.6	32.7	33.3	32.0	34.2			28.8	33.1
" c	25.6	32.4	25.9	33.1	24.2	32.5	30.0	33.1	33.2	33.3	32.3	34.0			28.6	32.8
" d	25.1	31.4	25.5	32.5	23.8	32.4	30.2	32.9	33.2	33.1	32.4	34.0			28.4	32.7
" e	24.6	31.6	25.4	32.6	23.9	32.1	30.1	32.7	32.4	33.5	32.4	33.8			28.1	32.7
12	30.0	32.6	30.4	33.0	31.1	31.3	32.5	33.6	30.8	32.6	31.3	33.4			31.0	32.8
14	30.5	32.9	30.3	33.5	30.0	31.8	30.7	32.7	30.4	32.0	31.5	32.6			30.6	32.8
16	26.5	31.9	30.5	31.7	28.3	30.4	29.7	32.6	30.3	33.4	30.0	31.9			29.2	31.9
18	23.8	29.3	27.9	32.2	26.6	28.5	26.6	31.5	29.2	33.0	29.2	31.5			27.2	31.0
" a	23.3	28.4	24.9	33.2	23.6	28.7	24.0	32.4	28.3	33.0	25.3	31.2			24.9	31.1
" b	24.1	28.8	24.7	32.6	22.0	28.0	24.2	33.1	28.3	32.0	25.3	30.9			24.8	31.1
" c	23.5	28.0	24.8	32.2	23.0	27.1	23.4	32.0	28.0	33.1	25.7	30.5			24.7	30.5
" d	23.9	27.7	24.6	31.7	23.7	26.9	23.3	31.6	27.8	33.4	25.9	31.3			24.9	30.4
" e	24.8	27.2	24.4	31.7	24.0	26.6	22.9	31.1	28.0	33.1	26.1	31.1			25.0	30.1
13	30.8	32.7	29.4	32.5	30.6	31.5	31.9	33.6	30.3	33.3	30.9	33.0			30.6	32.8
15	27.5	33.3	29.6	33.4	29.8	31.5	30.7	32.1	30.8	32.6	31.3	33.9			29.9	32.8
17	26.8	30.7	29.4	33.1	29.1	30.6	29.7	32.2	29.7	33.2	29.4	33.1			29.0	32.2
18	23.9	29.5	26.4	32.3	27.1	28.7	26.5	32.2	29.0	33.0	27.5	31.7			26.7	31.9
" a	22.9	29.7	25.0	32.0	23.5	30.0	23.5	31.5	27.1	32.9	25.7	30.9			24.6	31.2
" b	24.0	30.4	24.7	32.7	22.0	29.0	24.2	32.6	27.2	33.0	24.9	31.6			24.5	31.5
" c	23.8	29.1	24.2	32.7	22.4	28.2	24.1	31.8	27.0	33.0	25.4	30.9			24.5	30.9
" d	24.1	28.7	24.1	32.6	22.7	27.0	24.0	32.7	27.1	33.0	26.2	31.9			24.7	30.9
" e	24.1	28.2	24.7	32.7	22.1	26.2	23.6	32.2	27.1	33.0	25.2	31.6			24.4	30.6

"vasoconstrictor gradient." Variations in the gradient were most evident at the tips of the fingers and toes. We consider measurements of the skin temperature at these points to be particularly informative of changes of vasomotor tonus. Under well-controlled conditions the measurement of the amplitude of such variations can be used to record stimulation or depression of the sympathetic nervous system.[6]

Since lower peripheral skin temperatures were found on women than on men it was evident that the peripheral vasoconstrictor gradient was more marked in the women. Benedict and Root[7] observed this same phenomenon

and suggested that the difference between the sexes might be due to the fact that women ordinarily wear lighter clothing on the extremities.

With the object of expressing the skin-temperature measurements of their studies at a constant environmental temperature Morton and Scott[8, 9] adopted the correction figure of 0.3° C., as presented by Vincent,[10] to be added or subtracted for each degree of variation of the room temperature below or above 20.0° C. Vincent's constant was founded on the basis of 360 observations on the back of his own hand. Important objections to



AVERAGE SKIN TEMPERATURE OF:
A.-SIX NORMAL WOMEN EXPOSED TO AVE. RM. TEMP. 24.8° C FOR ONE HOUR.
B -ENVIRONMENTAL RESPONSE IN WOMEN.
C -SIX NORMAL MEN EXPOSED TO AVE. RM. TEMP. 25.0°C FOR ONE HOUR.
D -ENVIRONMENTAL RESPONSE IN MEN.

Vincent's work have been made with criticisms based on the choice of the site for the point of investigation, on the method of measuring the skin temperature, and finally on the lack of consideration of the clothing. Cobet[12] concluded that the general applicability of Vincent's formula could not be accepted.

Reichenbach and Heymann,[11] in their work on the possible correlation between skin temperature and air temperature, developed a formula expressing the relation of the skin temperature of a dead body with a constant source of inner heat, to the temperature of the surrounding air. Their simplified formula corresponded fundamentally to the formula of Vincent. It was realized at the time of the development of the formula that on applying it to the living body the skin circulation was a local variable factor not

taken into consideration, as was also a possible variation in conduction from the inner temperature. To avoid these two factors as much as possible, Reichenbach and Heymann chose the forehead for the point of their investigation. Our data show that the skin temperature of the hands and feet presents the greatest magnitude of variations of all skin temperatures of the body, undoubtedly due to frequent variations in vasomotor tonus. Therefore, the hands and feet with the sympathetic nervous system control intact would be the worst possible location to expect to apply a constant figure for a correlation of skin temperature with environmental temperature.

The data from the covered period, recorded in columns B in Tables I and II and the average in Chart 1, showed:

(1) The skin-temperature measurements for the men were approximately the same on the trunk and the extremities, generally above 33.0° C. and more commonly between 34.0° C. and 35.0° C. Rather marked sweating occurred on most of the subjects.

(2) The response in women varied somewhat from that in men. The skin temperature of the well-covered trunk points of the women closely approximated the 33.0° C. to 34.0° C. of the trunk points on the men. The skin temperature of the upper extremities of women were slightly lower than those of the men, the average, however, being above 32.0° C. For the lower extremities the difference between the sexes was more marked, the average for the women being above 30.0° C. Excepting* the female subjects A. B. and M. G., the level of the whole average response for women would be above 32.0° C.

Comment.—Benedict,[13] in 1925, demonstrated the high uniform skin temperatures prevailing after a night in bed with adequate bed clothing. We have produced the same result in a shorter period of time, probably considerably aided by the rubber sheet.

Several investigators[14, 15, 16, 17, 18, 19, 20, 21, 22] have shown that in normal individuals the release of peripheral vasoconstriction by paralysis of the sympathetic nervous system with local or general anæsthesia results in skin temperatures about 33.0° C. or above in the area involved. Morton and Scott[18] consider this temperature to be the low limit of the normal level when all vasoconstriction is removed and have applied to it the term "normal vasodilatation level." Brown[22] previously showed that with an induced fever high uniform skin temperatures prevailed. It is evident that approximately the same skin temperatures were reached in our normal subjects in

* In the series of fifteen women studied, five showed definitely lower peripheral skin temperatures at the end of the covered period than the remainder of the group. These five stated that their feet were usually cold after a whole night in bed well covered. Their peripheral pulses were normal to examination. The inclusion of two of these subjects, A. B. and M. G., in the data presented reduced the low level of the foot points from 32.0° C. to 30.0° C.

response to the environmental conditions of the covered period.* This result is in accordance with the factors of the physical regulation of body temperature. At high environmental temperatures the maximum amount of blood is brought to the surface of the body for the dissipation of heat.

A comparison of the data of the exposed period with the covered period showed:

(1) The number of degree rise in the skin temperature from the exposed to the covered period was approximately the same for both sexes. The level in both instances, however, was lower for the women.

(2) With the increase in the environmental temperature of about 10° C. the skin temperature of the trunk points increased only 1.0° C. to 1.5° C., the upper extremity increased 2.0° C. to 5.0° C., the lower extremity increased 2.0° C. to 7.0° C. The greatest changes took place in the hands and the feet.

Comment.—As already stated, the skin plays a very important part in the dissipation of body heat. About 65 per cent. of the total skin surface is on the extremities.[23] The greater response of the extremities to the increased environmental temperature suggests that the extremities, thrust out into the environment from the more vital trunk and head, play a greater regulating part in the dissipation of heat than the ratio of their surface area to the total. The control of this dissipation of heat from the extremities is probably one of the main functions of the "vasoconstrictor gradient." This important part played by the extremities in the regulation of body temperature is not generally recognized.

From the study of the environmental response of the normal individuals we wish to emphasize the fact that with the high temperatures prevailing under the covers high uniform skin temperatures were obtained which were approximately at the "normal vasodilatation level."

PART II: PERIPHERAL VASCULAR OCCLUSIONS

Having established the physiological response in normal individuals to the environmental conditions presented, the procedure was carried out in a similar manner on a number of individuals with symptoms of peripheral vascular occlusion. This application was made on the theoretical grounds that with the high environmental temperature under the coverings the physical regulation of body temperature would result in a maximal dilatation of the peripheral blood-vessels, and that the failure of the skin temperature to reach the "normal vasodilatation level" would be due to organic vascular occlusion. Morton's and Scott's[18] term of "occlusion or obstruction index" was used to indicate the degree of failure of the skin temperature to reach the normal level.

In studying the environmental response in conditions of disease the following points were especially considered:

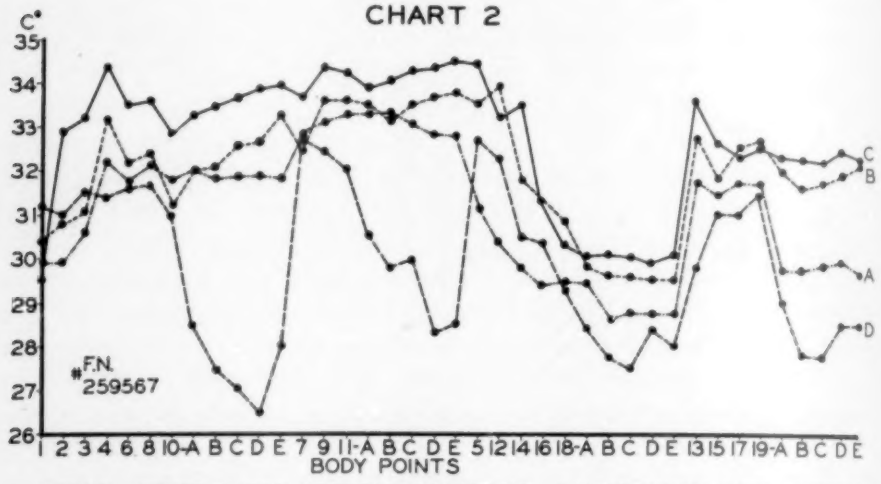
* See footnote † on page 719.

(1) The value of the procedure in differentiating spastic from organic peripheral vascular occlusion.

(2) A comparison of the result of this test with other differential tests.

(3) A comparison of the skin temperatures obtained with the test with those following sympathectomy.

In Chart 2 are shown the results of skin-temperature studies on a senile man, aged sixty years, who complained of pain in the right foot and who had a small area of gangrene about the right great toenail. The environmental response B showed a failure of the skin temperature of the right foot to reach the normal level of 33.0° C. and an occlusion index of about 3.5.

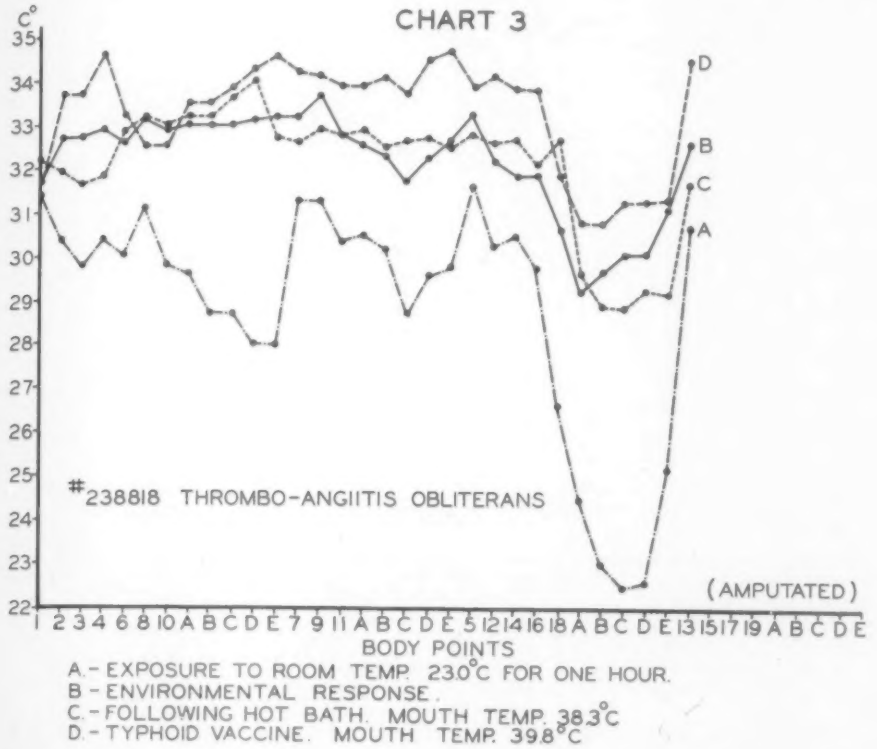


AGE 59 GENERALIZED ARTERIO-SCLEROSIS GANGRENOUS AREA ABOUT RIGHT GREAT TOENAIL.

A. - EXPOSURE TO ROOM TEMP. 25.0°C FOR ONE HOUR.
B - ENVIRONMENTAL RESPONSE
C - TYPHOID VACCINE. MOUTH TEMP. 39.1°C
D - SPINAL ANESTHETIC

The skin temperatures of the left foot were nearly up to the normal level. A comparison for the right foot of curve B with the exposure temperature curve A showed a difference of about 1.0° C., indicating a negligible degree of vasoconstriction present. There was an extremely close correspondence of the environmental test with the skin temperatures following typhoid vaccine indicated by curve C. With spinal anæsthesia the skin temperatures were generally lower, the levels for both feet were approximately the same, showing, according to this test, the same degree of circulation. With the environmental response, with typhoid vaccine and clinically, the circulation of the left foot was definitely better than that of the right. The markedly lower skin temperature of the hands, after the spinal anæsthetic, was probably largely due to the psychic trauma associated with the administration of this anæsthetic. The results of the tests clearly showed that marked organic vascular occlusion was present in the right leg.

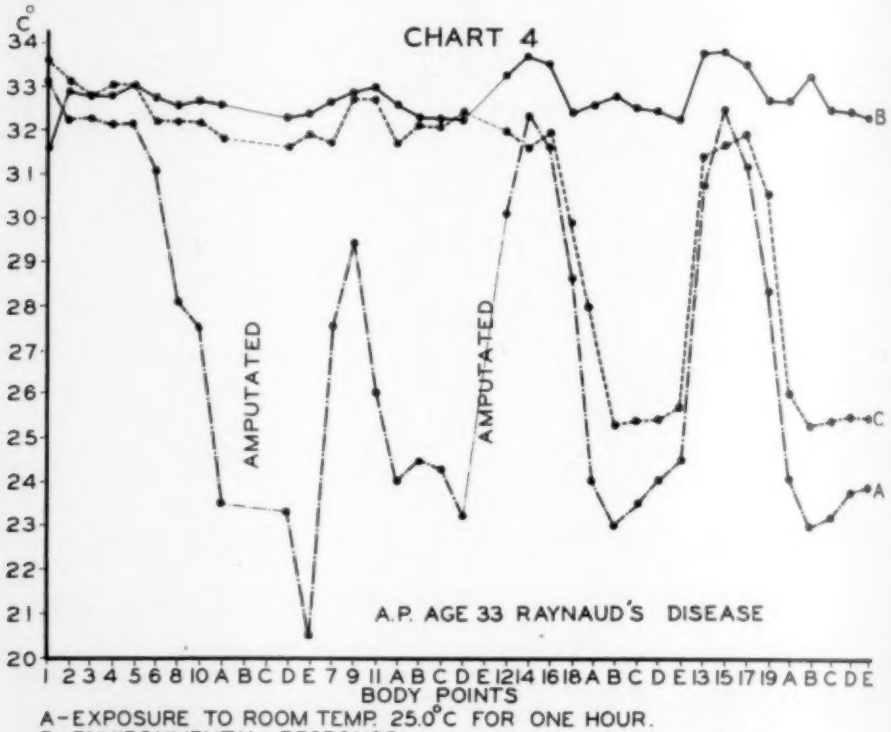
Chart 3 presents the result of skin-temperature studies on a male patient aged thirty-five years with thrombo-angiitis obliterans who complained chiefly of pain in the right forefoot. A left low thigh amputation had been done for extensive gangrene of the left foot. The rise in the skin temperature of the right foot from curve A to curve B indicated the production of a considerable degree of vasodilatation as the result of the environmental test. That definite organic occlusion was present was shown by the failure of the skin temperature of the right foot to reach 33.0° C., the occlusion index being approximately 2.5. The result obtained with the environmental test compared favorably with the result of the other tests shown in curves C and



D. Some vasoconstriction superimposed on a marked organic occlusion made the wisdom of a lumbar sympathectomy doubtful. However, this was carried out and gave the result prognosticated by the tests.

In Chart 4 the application of the environmental test to a typical case of Raynaud's disease involving the hands showed in the rise from curve A to B the release of a rather marked degree of peripheral vasoconstriction. Curve B is approximately at the normal level, demonstrating the presence of little or no organic occlusion. Following a cervico-dorsal ramusectomy and ganglionectomy, skin temperatures, as shown in curve C for the affected area, closely approximated the prediction of the test.

Chart 5 presents the application of the environmental response in a girl aged nine years with a peripheral vascular disturbance associated with paralysis of the left leg from an old anterior poliomyelitis. The entire absence of organic vascular occlusion is shown by the level of the skin temperatures in the environmental response reaching the normal in curve B. Following a left lumbar sympathetic ganglionectomy the skin temperature of the left foot, as shown in curve C, closely approximated the level of the environmental response.

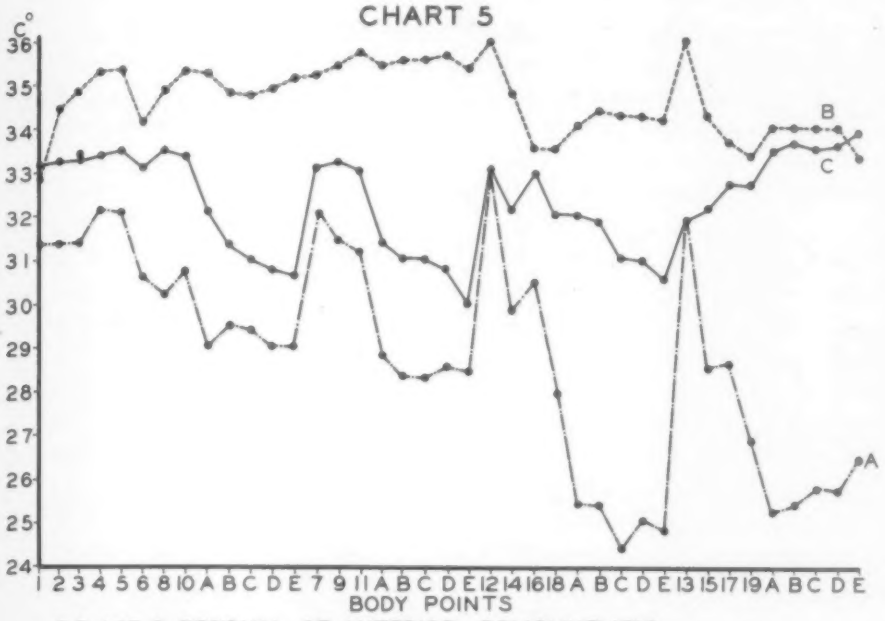


A-EXPOSURE TO ROOM TEMP. 25.0°C FOR ONE HOUR.
B-ENVIRONMENTAL RESPONSE.
C-FOLLOWING CERVICO-DORSAL RAMUSECTOMY AND GANGLIONECTOMY. EXPOSURE TO ROOM TEMP. 25.5°C FOR ONE HOUR.

Comment.—During the past two years in a study of thirty individuals with clinical evidence of a peripheral vascular occlusion, there was only one patient on whom the results obtained with the environmental test neither agreed with the clinical impression, nor with the result of other tests used. This patient, a male aged forty years, had marked vasoconstriction of traumatic origin, secondary to a fracture of the first metatarsal three years previously. Maximal rises in temperature of the extremities occurred with spinal anæsthesia and a posterior tibial nerve block. The routine environmental response did not reach the normal level in spite of evidence that this should have occurred. The test was repeated with the addition of a hot-water bottle at 50.0° C. to the feet for the first half-hour of the covered period with a result at the end of the hour in accord with the other tests.

A lumbar sympathectomy ganglionectomy was performed with a maximal response. The impulses from the sympathetic system were apparently of such force that they did not respond in the hour period.

The other tests presented for the differentiation of spastic from organic vascular occlusions are well known and have been adequately discussed elsewhere.[16, 17, 18, 19, 20, 21, 22] The value of many of them has been proven by long use. From observations based on these tests, peripheral vascular occlusions have been divided into three main groups:



D.P. AGE 9 RESIDUAL OF ANTERIOR POLIOMYELITIS
A.-EXPOSURE TO ROOM TEMP. 24.0°C FOR ONE HOUR.
B-ENVIRONMENTAL RESPONSE
C-FOLLOWING LEFT LUMBAR SYMPATHETIC GANGLIONECTOMY
EXPOSURE TO ROOM TEMP. 25°0 C FOR ONE HOUR.

Group I.—Those cases in which no change or slight change occurs in the skin temperature as a result of the test, indicating organic occlusion and no vasospasm. A sympathectomy would be of no value to these individuals. This group is composed largely of cases of advanced peripheral arteriosclerosis and late thrombo-angiitis obliterans.

Group II.—Individuals in which the skin temperature rose to the normal vasodilatation level for the test used, thus demonstrating the absence of an organic occlusion as a basis for the disorder. A sympathectomy offers the greatest possibility of relief in this group. These disorders comprise Raynaud's disease, scleroderma, and a number of less marked vasospastic conditions associated with residual paralyses of anterior poliomyelitis, with spastic paralyses, with chronic arthritis, and with some cases of trauma.

Group III.—Presents a combination of the factors of Group I and II.

Here a rise in the skin temperature occurs as a result of the test, but not to the normal level, indicating the presence of some organic occlusion and some vasospasm. The value of a sympathectomy is determined by the relative amount of organic occlusion present. The early cases of thromboangiitis obliterans are in this class.

None of the tests previously presented is entirely free from disagreeable features and many of them require hospitalization. We do not consider their general application to be as simple as the one we are advocating. Fundamentally, the environmental response and the other differential tests are means of determining the presence or absence of organic vascular occlusions. The presence of vasoconstriction is also shown but whether or not this is pathological can be determined only by clinical observations. Again, so many factors may cause a variation of the degree of peripheral vasoconstriction present that a measurement during exposure of the body to a moderate room temperature reveals nothing concerning the magnitude of the process at other times. It therefore does not seem worth while in actual practice to expose the patient for the hour period. The important measurements are those made in response to the high environmental temperature during the hour under covers as these are the indices of the presence or absence of organic occlusion. Adopting this view we frequently have shortened the test to the covered-hour period. We have occasionally used room temperatures of 30.0° C. or more as a substitute for the rubber sheet and blanket coverings but it has been slower and less reliable in producing a uniform peripheral vasodilatation. The physiological response of the peripheral vessels to high environmental temperatures should be constant, the coverings are simply a convenient method of providing a fairly uniform suitable environment.

SUMMARY.—A simple method of study, requiring no special apparatus excepting a thermocouple for the measurement of skin temperatures, is presented as a test for the presence and degree of organic obstruction in cases of peripheral vascular occlusion. The test is based on the factors of the physical regulation of body temperature and fundamentally is the skin temperature response to high environmental temperatures.

In Part I the skin temperature response of normal subjects to varying room temperatures and to the high environmental temperatures prevailing under a rubber sheet and woolen blankets was established. Under the latter condition uniformly high skin temperatures were found. These temperatures were approximately at the "normal vasodilatation level" of 33.0° C. obtained by other investigators as a result of paralysis of the sympathetic nervous system with general or local anæsthesia. Evidence was presented that the extremities play an important part in regulating the dissipation of body heat in response to changes in the environment by varying the amount of vasoconstriction or vasodilatation.

In Part II the application of the procedure to subjects with peripheral vascular occlusions showed that a failure to reach the normal vasodilatation

level was due to the presence of organic vascular obstruction. In twenty-nine out of thirty cases studied, the level of the skin-temperature response to the covered period was found to be in agreement with that of other tests advocated for the differentiation of spastic from organic vascular occlusions. The skin temperatures of the extremities following a sympathectomy were always at the level predicted by the environmental response.

Ordinary clinical observations furnish fairly accurate information as to the type of occlusion involved in any case of peripheral vascular deficiency. If the result of the environmental response is contrary to the clinical impression, corroboration may be obtained by the use of the other tests.

The ease of clinical application, without danger and with little inconvenience to the patient, recommends the test of environmental response.

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THE GENERAL CARE OF PERIPHERAL VASCULAR DISEASES

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In the excitement of new ideas and discoveries with respect to the etiology, diagnosis and treatment of peripheral vascular diseases, enthusiasm for new procedures has all too frequently resulted in discarding or ignoring many of the simple but fundamental principles of treatment which may be of the greatest value. Generally speaking, it is a common fault to discard abruptly the old and to embrace wholeheartedly the new methods of treatment. As a result, many new procedures become overworked, prove disappointing, are almost discarded and then gradually assume their places as valuable adjuncts to the existing therapy of disease. This weakness is particularly manifest when we are dealing with difficult problems in which, at best, our efforts often prove discouraging.

The treatment of peripheral vascular lesions is a difficult problem. In recent years it has become an active challenge to many investigators and notable advances toward its solution have been made. However, the fundamental nature of many vascular lesions seems to me to indicate that in most instances we can only help or ameliorate; that we cannot cure the underlying causes. In such cases it becomes advisable to utilize all procedures that may be helpful, to supplement our major treatments with all those minor details which may be of value in preventing or curing some of the consequences of these vascular lesions. It is my desire to stress the importance of what may be termed the petty details in the treatment of these conditions, for it is our belief that the great majority of patients do not often fully realize their value and all too frequently neglect details of treatment which, if faithfully observed, would prevent many complications.

It is often a difficult matter to make a patient realize the importance of the many precautions and details of treatment that should be observed; it is still more difficult to make him use them constantly and intelligently. Fortunately, almost every patient can be made to understand the reason for the things that he is advised to do if only the doctor will take the time and patience to explain. For examples, it should not be difficult to make a patient know that a reduced circulation means impaired nourishment to tissues and that the many things that he is told to do with respect to position and exercise of his extremities, the avoidance of cold, the care of the skin, *etc.*, are efforts to keep the nourishment of his tissues up to the maximum amount that can be obtained; that tissues with deficient nourishment cannot heal readily nor combat infection normally and that consequently any abrasion or infection of the skin should be given extraordinarily good care; that each arterial spasm leaves some permanent damage to tissues; or that infected

vessels should no more be traumatized than boils or other infections. Yet, when the reasonableness of advice has been made perfectly clear and understandable, the actual observance of it must be watched and checked until one is sure that he has obtained the patient's maximum interest and coöperation. General instructions will not be carried out until the details have been so frequently checked that they become a matter of routine and constant consciousness on the part of the patient. Commendation, of course, is helpful to secure interest and coöperation, but usually it is quite essential to observe that some detail of treatment might be improved or changed at each visit. "The feet are cold; you had better wear two woolen socks during this cold weather." "The skin is somewhat rough about the heel and I think you can grease that part a little more thoroughly." "The seam of your sock is making a groove on your toe or foot; you had better have some seamless ones knitted." "A quart of water is not enough; you should not drink less than three quarts in the twenty-four hours." "The end of your toe looks a little white as if a blister may be going to form; you should stay in bed for a couple of days." "These shoes are too tight; you must get larger ones." "How much do you move your toes when you are standing?" "An electric pad in your office would be helpful." These are but a few of the many ways that one may keep a patient interested in these details until they become a matter of a fixed routine with him. A good index of one's success along these lines is the development of ideas or the offering of suggestions on the part of the patient. His interest is then definitely aroused; frequently he makes real contributions toward the treatment of his own condition. The treatment of peripheral vascular lesions becomes most effective only when there is complete coöperation of the patient.

The fact that the vast majority of cases of peripheral vascular diseases are seen or diagnosed only after some serious complications, such as infection and gangrene, have appeared, should lead to a determined effort of the medical profession to make earlier diagnoses and, thus, to institute treatment and to enlist the patient's coöperation which would undoubtedly reduce the incidence of complications that so frequently mean the loss of extremities. The early adoption of a routine care and the simpler treatments would make unnecessary many amputations; many patients who now lose extremities would live out their lives without serious or tragic peripheral handicaps. The routine examination of all peripheral vessels would result in much earlier diagnoses; the true nature of many cases that are now treated for weeks, months and years for pain, fallen arches, and cramps would be established. If it were the rule to record the pulse from an examination of the pedal rather than the wrist pulses many more cases of early vascular trouble would be detected.

It is important to determine the level of a resting extremity, which will result in the optimum circulation. A little reflection on the various grades of peripheral vascular deficiency makes it obvious that this optimum level must be determined for each individual case. The actual force behind the

blood circulating through the peripheral arteries is subject to a wide variation; it is probably never identical in any two cases. A fairly accurate idea can be determined by the use of the Pachon oscillometer but this instrument is unfortunately at the disposal of very few doctors. A less accurate but practical idea of the level of optimum circulation can be obtained from observations on the fullness of the veins when the extremity is put at

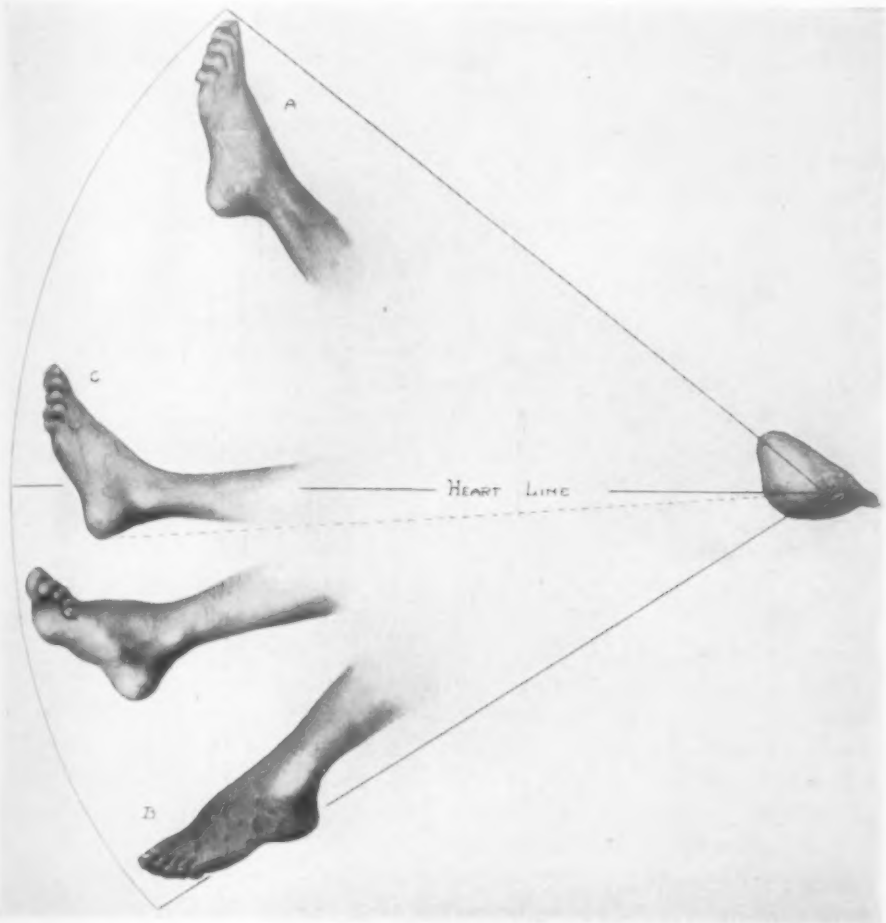

FIG. 1.—Illustration of the effect of position, with respect to the heart, upon the circulation of a foot in a case of peripheral vascular disease. Too great elevation above the heart is far more detrimental to the circulation than is a similar degree of dependency. (A)—The foot is pale and cadaveric; the veins are collapsed and produce grooves in the skin. (B)—The foot is congested; the veins are distended and produce elevations of the skin. (C)—Position of optimum circulation. The veins are neither distended nor collapsed. This level, with respect to the heart, varies with the degree of circulatory embarrassment and must be determined for each case by gradually elevating the foot from position B toward A and noting at what level the effect represented in C occurs. It is always somewhat below the level of the heart.

different levels with respect to the level of the heart. A foot that is allowed to hang over the side of the bed may become congested and cyanotic and the veins of it markedly distended. The effectiveness of the feebly circulating blood becomes reduced by the back-pressure of the venous blood and

the tissues of the foot suffer a reduced nourishment. If, on the other hand, the foot is elevated above the level of the heart it becomes blanched and cadaveric in appearance and its veins become collapsed, usually appearing as grooves in the skin. The weight of gravity of the column of arterial blood is seriously reducing the amount of blood that can be forced into the capillary bed and the tissues suffer a reduced nourishment. In the one instance it is the back-pressure of the venous blood that is harmful; in the other it is the back-pressure of the column of arterial blood. Somewhere between these two extremes is to be found the point of maximum circulation and consequently the greatest nourishment of tissues. We believe this point to be at the level where the veins are neither collapsed nor distended, when they are visible and apparently on the same level with the surface of the skin. This can be determined by the slow elevation of an extremity that has been allowed to hang down until the veins become fully distended. At a certain point, usually three to six inches below the level of the heart, the pressure within the veins can be seen to give way suddenly. Near to the point of this observation they will assume a capacity that neither distends nor retracts the skin. (Fig. 1.) This is an observation that the patient can make and in which he takes a great interest. Once the level of optimum circulation has been determined and the patient made to realize its importance he will usually endeavor to place his affected extremities at the best level whenever they are at rest. Many of my patients try to observe this position of optimum circulation whenever they are sitting or lying down—in the library, office and at the dining table, on the couch and in bed.

For some reason there is a fairly general impression that in cases of peripheral vascular disease the affected extremities should be elevated well above the level of the heart. In search of a reason for this practice I have wondered if it has not been adopted from the practice of high elevation of badly infected or œdematous normal extremities. The problems are, of course, in no way similar. There can be no question that many extremities are unnecessarily sacrificed as a result of rest and elevation far above the level of optimum circulation. It is difficult for me to refrain from criticism or comment when I visit hospitals and see all cases of arteriosclerotic and Buerger's disease of the extremities lying in bed with the affected parts white and cadaveric elevated on three and four pillows far above the level of the heart. Gangrene in many cases is certainly being hastened by this rather general practice.

It is usually easy to demonstrate to a patient the value of a certain amount of exercise whenever infection and gangrene are not a contra-indication. Voluntary movement of the ankle and toes will often cause a striking improvement in the color of an affected foot that has been allowed to hang still until it becomes red and cyanotic. We make our patients stand for a few minutes and then observe for themselves the improvement which comes with movement of the toes and ankles. The congestion is usually accompanied by a subjective sensation of tingling or tightness. With this

knowledge the coöperative patient will always move his toes and feet whenever he experiences this sensation. He soon learns that it comes most often when he stands or sits still. The harm of too much exercise and the meaning of the pains of intermittent claudication should also be explained.

In our experience it is best to require a short period of hospitalization in order to teach patients, when indicated, to carry out accurately the valuable exercises of Buerger and Allen. The cycles of these exercises in which time is devoted to heat, dependency with exercise and elevation are, of course, familiar to everyone. They should be a most important part of the routine of the patient's self-help. In addition to their unquestioned value they make the patient conscious of the care and duty he owes himself.

Circulation is unquestionably better when the skin is soft and delicate. It allows the freest breathing which normally takes place through the skin. It not only reduces the dangers of infection incident to cracks and calluses but it allows a better circulation than is possible when the skin is thickened, nonpliable and binding. Careful washing and greasing or oiling of the skin should be persisted in until it becomes as nearly like a child's skin as it is possible to get it. In the beginning of treatment this may necessitate treatment of the skin twice daily until the calluses and thickened, cornified epithelium disappear. It does not seem to matter much what lubricant is used; we usually employ cocoa-butter or lanoline and insist that it be rubbed into the skin until it seems to disappear. It is surprising how much enthusiasm the patient will take in the care of his skin if he fully understands its importance and gets the proper recognition for his efforts.

The vast majority of the complications of peripheral vascular disease occur during cold weather. Although this is true for both the degenerative and inflammatory processes (of the vessels) it is especially true in the angiospastic conditions. If then one can institute treatment or a mode of life which will, in a large measure, obviate the harmful effects of cold, the dangers that these patients constantly run may be lessened. One cannot accept the patient's assertion that his feet, for example, are warm. His subjective appreciation of warmth and cold is most untrustworthy. Many times a patient will say his feet are warm when if he himself feels them with his hands he will appreciate that they are icy cold. Woolen socks with or without fleece-lined shoes should be insisted upon until the feet perspire, feel uncomfortably warm subjectively and definitely warm objectively. As a result of the doctor's persistence and suggestions the determination to keep his extremities warm often becomes the patient's hobby. I am told by Dr. George Lawson, of Roanoke, Virginia, that he has a patient with severe Raynaud's disease, who for many years has not had a single arterial spasm. The skin of his hands has become soft, pliable and very delicate; the stiffness of the fingers and infiltration of the tissues have disappeared. His work is inside; under no conditions will he subject his extremities to cold. When he goes outside his hands are always covered with previously warmed fleece-lined or woolen gloves; he takes scrupulous care in the washing and

greasing of his skin. A patient of ours who has apparently recovered from an attack of severe thrombo-angiitis obliterans has had made a pair of fur-lined trousers (Fig. 2) to keep his legs warm when he is riding horseback or hunting ducks. By means of woolen socks worn day and night, electric heaters in his car and at the office, he never allows his feet to get cold. At one time there were weeks when it seemed certain that he would lose his leg at any time; now he plays golf and tennis, rides and hunts as he desires. Another patient suggested and secured the fleece-lined shoes illustrated in Fig. 3. These are just a few examples of the fruits of interested and coöperative patients. Do not discourage this initiative and interest. Let patients devise and tell you the very things you would like them to do. Success will be greater because these things are their ideas and the situation can always be handled so as not to

FIG. 2.

FIG. 3.

FIG. 2.—Sheep-skin boot and legging designed by a patient with thrombo-angiitis obliterans to keep his foot and leg warm when riding or hunting.

FIG. 3.—A shoe lined with wool suggested and used by a patient to keep his feet warm during the winter months.

lose patients' respect and admiration. Besides, how many doctors will devote the time to details, the patience and effort to accomplish these ends as well?

There do not appear to be any harmful effects from overheating. On the contrary, it is our belief that sweating of the extremities is a good thing, not only to improve the delicacy of the skin and the inflammatory processes beneath it, but to help the actual nourishment of the tissues. Certainly it seems to hasten the disappearance of the board-like rigidity of the toes and fingers.

It is scarcely necessary to stress the seriousness of wounds and infections of the extremities in association with peripheral vascular disease; it is well appreciated. It could be better realized by patients to the end that they would seek treatment or advice for the most trivial wounds, blisters, infec-

tions or discolorations of the skin. No matter how slight they may be or appear to be it is a good policy for patients to realize that they mean stopping work and going to bed, with the most meticulous care of them until they are completely healed. Unfortunately, through ignorance, a great many patients do not seek advice until some innocent-looking lesion has developed into a dissecting and spreading infection. The dangers incident to the cutting of calluses and nails have been stressed by Allen and many others; it is of the utmost importance that the patient fully understand them. When, in the care of the feet and hands, any blood is drawn, patients should seek the treatment of a doctor until they become thoroughly familiar with what to do.

FIG. 4.—Illustration of dependent drainage in order to lessen the spreading of infection from an infected toe into the sole and dorsum of the foot.

It is considered beyond the scope of this paper to discuss the details incident to the performance of amputations and the treatment of infected wounds. These vary somewhat in almost every clinic. Generally speaking, the accepted procedures that the surgeon knows and uses best should be employed. For infections we prefer wide-open wounds and the use of Dakin's solution. In order to lessen the spreading influences of gravity we usually adopt the position illustrated in Fig. 4 in the case of amputated infected toes where the tendency of the infection to go into the sole of the foot is very strong. In the amputation of infected toes and fingers we have been anchoring the tendons to their sheaths before dividing them. (Fig. 5.) It should tend to lessen the dragging of infection upward if the proximal end of the divided tendon is not permitted a wide retraction.

We have had a few instances which strengthen our belief in the fundamental principle that trauma, in the presence of inflammation, may do harm. In thrombo-angiitis obliterans, especially, the vessels are inflamed and in the more acute cases the patients are frequently conscious of pain in the popliteal and other vessels. In one instance the taking of blood-pressures in the affected leg was followed by damage to the artery and rather sudden disastrous results. In addition to the direct trauma that a tourniquet may do to diseased vessels the temporary stasis of blood distal to it should certainly encourage the extension of a thrombotic process. The possible trauma incident to certain forms of exercise (example, horseback riding) or to passive massage should always be considered.

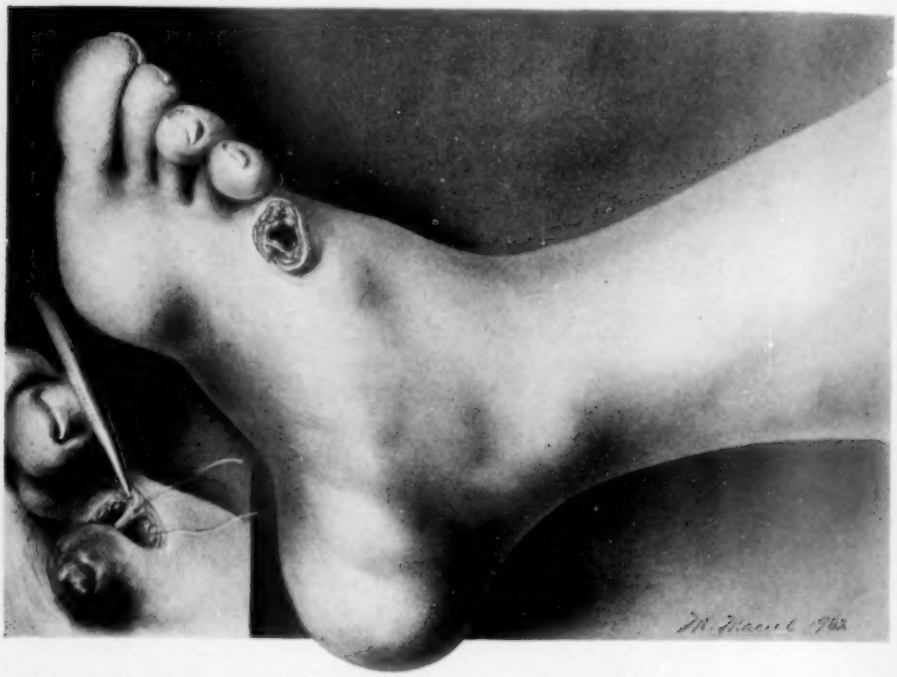

FIG. 5.—Illustration of a method of anchoring tendons to their sheaths when amputating infected or gangrenous toes. This method avoids a wide retraction of the tendons and probably lessens the spreading of infection into the foot.

In the cases of amputation for gangrenous and infected extremities, not associated with primary vascular disease, we have usually employed the use of double tourniquets, performing the amputation between them. (Fig. 6.) This technic prevents the back-flow of the blood and lymph from the infected extremity into the field of operation and thus should lessen the chances of infecting the operative wound. The necessary manipulation of the infected area during the procedure of amputation probably throws a great many organisms into the blood and lymph which would be spilled into the operative field if the distal tourniquet were not used. In those cases of amputation necessitated primarily by vascular diseases, we do not take the risk of the possible damage of the proximal tourniquet; the distal one alone is used.

The fluid intake of patients with peripheral vascular disease should be very large. A simple statement to this effect is not as efficacious as to require that a daily written record be kept. Only after a patient has established a fixed routine of drinking water by actual measurement can he be trusted to take the four thousand or more cubic centimetres that should be drunk in each twenty-four-hour period. If the intake by mouth is constantly large the giving of fluids subcutaneously, intravenously or by duodenal tube becomes less necessary.

In some instances the blood-pressure may be elevated and the circulation beneficially accelerated by the use of thyroid extract. Many patients with peripheral vascular disease are found to have a lowered basal metabolic rate.

In the cases of peripheral vascular disease it would appear just as important to try to eradicate all foci of infection as it is to do so in cases of arthritis, myositis or neuritis. This procedure would appear especially logical in the instances of thrombo-angiitis obliterans and other inflammatory

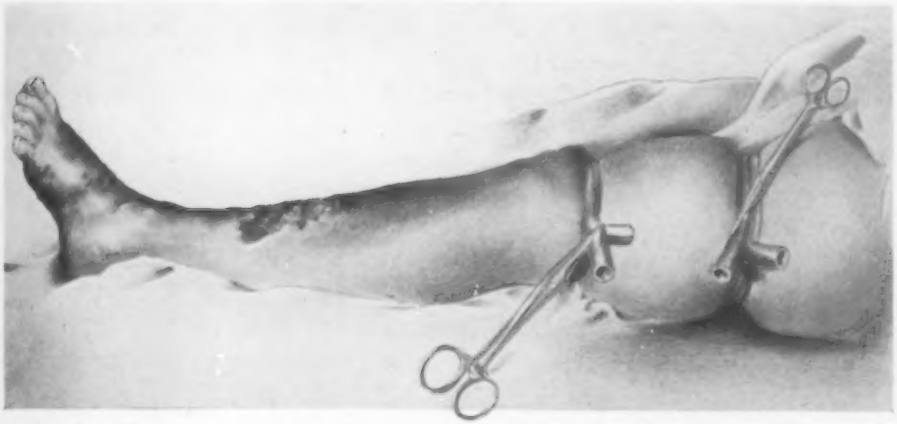

FIG. 6.—Illustration of the use of two tourniquets to lessen infection, through venous and lymphatic return, of the stump when amputating infected extremities not associated with peripheral vascular diseases. In the latter case the distal tourniquet alone is used.

conditions in which, as is usually the situation, no definite portal of entry for the infection can be found. In some cases we have tested patients for their sensitivity to vaccines made from their own organisms recovered from the sinuses, teeth and intestines, and have treated them with vaccines to which they are most sensitive. As usual, it has been difficult to evaluate this vaccine therapy.

In view of the uncertainty and contradictory evidences of the harmful effects of tobacco, it has become our policy to discontinue its use whenever it can be done.

This paper must not be construed to minimize the great value of employing operations upon the sympathetic nervous system or of giving foreign protein stimulation when indicated, nor of utilizing the various means of estimating vascular sufficiency by a study of skin and tissue temperatures under different forms of anæsthesia and foreign protein reaction and by

employing oscillometers, tourniquets, *etc.* The control of pain by means of drugs and peripheral anæsthesia has not been discussed.

An attempt has been made to emphasize the value of what might be called the details of the general treatment of peripheral vascular disease, which the author thinks are important but often overlooked. It may be objected that many of the things that have been discussed are impractical with the class of patients who seem to be most frequently afflicted, but with them much more could be done than is now being accomplished.

The specific nature of any given case might call for alterations of or additions to what has been discussed. In the inflammatory, spastic and toxic conditions which, with good care, tend to run a definite course toward spontaneous healing and the establishment of a more or less satisfactory collateral circulation it seems to me that the incidence of complications and amputations could be materially reduced by adhering to what has been designated in this paper "The General Care of Peripheral Vascular Diseases." I am not at all sure that a long period of bed rest would not be as useful in preventing the spreading and in hastening the healing of inflamed blood-vessels as it is in the case of pulmonary tuberculosis.

SUMMARY.—(1) In the management of peripheral vascular diseases it is of the utmost importance to secure and maintain the interest and active coöperation of patients. Fortunately, most of the therapy is reasonable and easily understood if only the time and patience are devoted to explaining its significance.

(2) The position of maximum circulation of the affected parts when at rest should be determined for each case. A simple method of determining this position is described. Too much elevation more effectively reduces nourishment and more frequently causes gangrene than does too much dependency.

(3) The effect of cold is evident from the high incidence of complications during the winter months. The affected extremities should never be allowed to become cold. Moderate sweating improves the texture of the skin and the nourishment of the tissues beneath it.

(4) By means of baths, oils and greases the skin should be made as soft and delicate as possible.

(5) The most trivial wounds and infections should be treated as major complications until they are completely healed.

(6) Any form of trauma to inflamed or diseased vessels should be avoided by both the patient and doctor. The possible dangers of the tourniquet and blood-pressure apparatus are discussed, as well as certain forms of exercise and passive massage.

(7) In order to teach patients the Buerger or Allen voluntary exercises a short period of hospitalization is probably desirable.

(8) Amputations performed between two tourniquets for gangrenous and infected extremities probably reduce the incidence of infection of the

stumps. If, for fear of damage to tissues and blood-vessels, the use of a tourniquet is contra-indicated, the distal tourniquet alone may be used.

(9) The fluid intake should be established and maintained on a high level.

(10) In some instances the use of thyroid extract may help to improve the circulation.

(11) All foci of infection should be eliminated.

(12) It is our policy to advise abstinence from the use of tobacco and alcohol.

(13) The routine examination of all peripheral pulses would result in earlier diagnoses of peripheral vascular diseases and would make possible the avoidance of many complications which are so frequently the direct cause of amputations.

OBSERVATIONS ON SYMPATHETIC VASOMOTOR PATHWAYS

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of New Haven, Conn.

During recent years there has been a widespread interest in the surgical treatment of a group of diseases which manifest themselves by a dysfunction of the sympathetic vasomotor system. While the good results following operative procedures have been steadily increasing, they have not always fulfilled expectations. This may be explained, in part, on the basis of poor selection of cases and as more exact means of demonstrating vasomotor dysfunction have been developed the results from operative procedures on the sympathetic system have accordingly improved. Another source of error has been the use of operative procedures by which the sympathetic vasomotor pathways have not been adequately removed or interrupted. This was particularly evident during the developmental phases of the surgery of the sympathetic nervous system. While the need for more exact operative procedures has stimulated investigation of the pathways by which these fibres reach the peripheral blood-vessels the central connections of the sympathetic ganglia have not in recent years received as much attention. It is the purpose of this paper to report some observations on the central connections of the sympathetic vasomotor fibres in man as well as in laboratory animals.

Case Record.—Symptoms suggesting Raynaud's syndrome with generalized vasomotor dysfunction and superficial gangrene of the right hand and left foot. Dorsal sympathectomy right arm and lumbar sympathectomy left leg. Relief of symptoms but six months later novocaine injection of peripheral nerves caused rise of temperature in right arm and left leg.

Admission.—March 17, 1931 (Unit No. A-849), Mr. A. B., aged forty years, referred by Dr. Wilder Tileston, of New Haven, with the complaint of pain and ulceration of the left great toe.

Anamnesis.—The patient, a plumber, had been in good health until 1927, when he noticed "rheumatism" in his legs. (Noted as stiffness and pain on arising in morning and relieved by exercise.) In 1929, he developed pain in the calves of his legs after walking about a hundred yards, the pain always being relieved by rest. These symptoms increased until about six months before entry to the hospital, at which time he consulted an orthopædist who prescribed arch supports which completely relieved the pain in his legs. Coldness of the feet was first noted in December, 1929, following severe exposure while out of doors. During the year preceding admission he had noted marked color changes of both the hands and feet. This was particularly marked in the feet after exposure to cold water, when they became very cyanotic. Four months prior to admission several small blisters developed on the first and fifth toes of the left foot. These blisters discharged a small amount of serum and on healing left a small pit in the skin which for some time remained tender. Some of the larger of these blisters developed into ulcerative lesions which healed slowly. Coincidental with the skin lesions he developed a dull throbbing pain in the left great toe.

Physical Examination.—This showed a rather undernourished man with no abnormal findings except in the extremities. The upper extremities were normal except for a few small blisters two to three millimetres in diameter on the index finger and thumb of the right hand. On the plantar surface of the left great toe, there was a partially healed superficial ulceration. The first and fifth toes showed numerous small scars in the skin at the base of the nails. The nails also showed evidence of retarded growth. There was no evidence of arteriosclerosis either on physical examination of all the palpable arteries or by röntgenographical examination. The dorsalis pedis arteries could not be palpated in either foot but there was good pulsation of the posterior tibial arteries. Röntgenograms of the feet showed slight atrophic changes of both the tarsal and metatarsal bones and some slight irregularity of the articular surfaces. All the other laboratory findings, including blood, urine and serological examinations, were negative.

Subsequent Course.—The vasomotor responses were studied in a constant temperature room by means of the Leeds and Northrup Multiple Point Temperature Recorders. These findings are shown in Chart I and in general demonstrated a mild type of vaso-

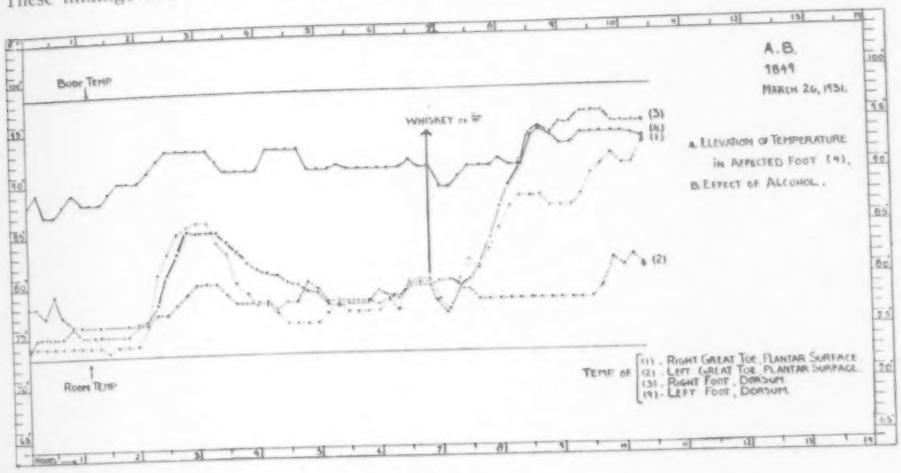

CHART I.

motor instability which was somewhat more marked in the lower extremities. The ulcers on the feet rapidly improved under a short period of conservative treatment, and the patient was discharged to await further developments. For a short while there was some improvement but again the symptoms returned worse than ever and he was advised to enter the hospital for sympathectomy. Two days before the date set for his second admission he entered the hospital with an attack of acute appendicitis. Following the removal of an acute appendix under ethylene anæsthesia the patient made an uneventful convalescence and was discharged home June 15, 1931, to return later for sympathectomy. During the next few months his appetite improved and he gained twenty pounds. He stated he had not felt so well for years and his symptoms of vascular disease completely disappeared. He continued to work at his trade as plumber, until September, 1931, when, coincident with loss of appetite and twenty pounds in weight, the vascular symptoms returned in an even more exaggerated form and he entered the hospital October 5, 1931, for sympathectomy.

During this last attack the lesions had become more pronounced in the upper extremities and especially in the right hand. The vasomotor disturbances were more pronounced in both the hands and feet and he now presented a fairly typical Raynaud's syndrome. Atrophic changes were pronounced in the left great toe and the right index finger, in both of which the skin was a tense shiny red and both presented ulcerations at the base

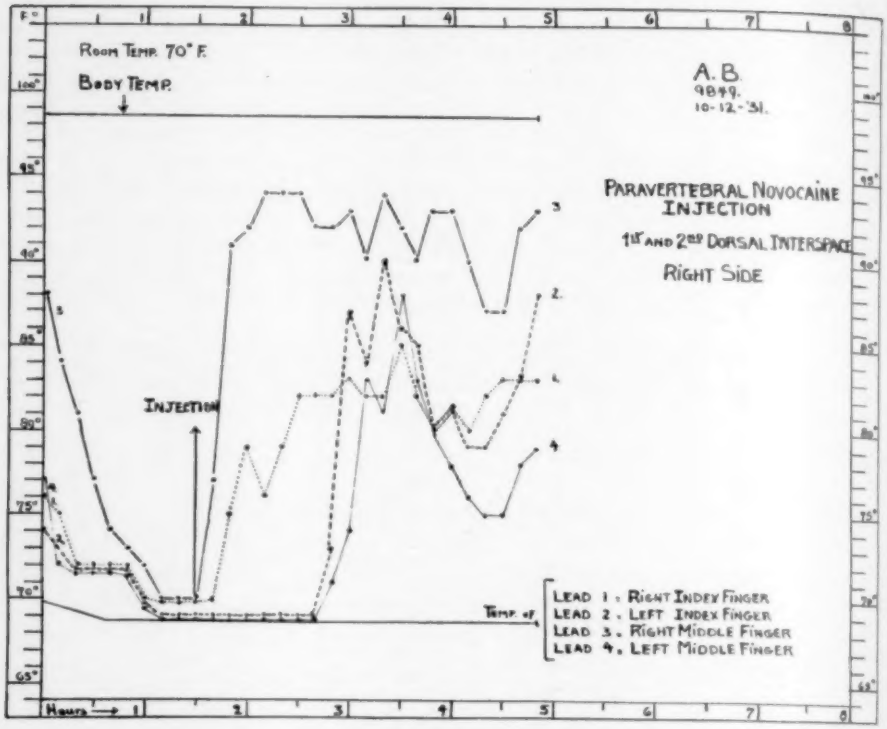

Chart II.

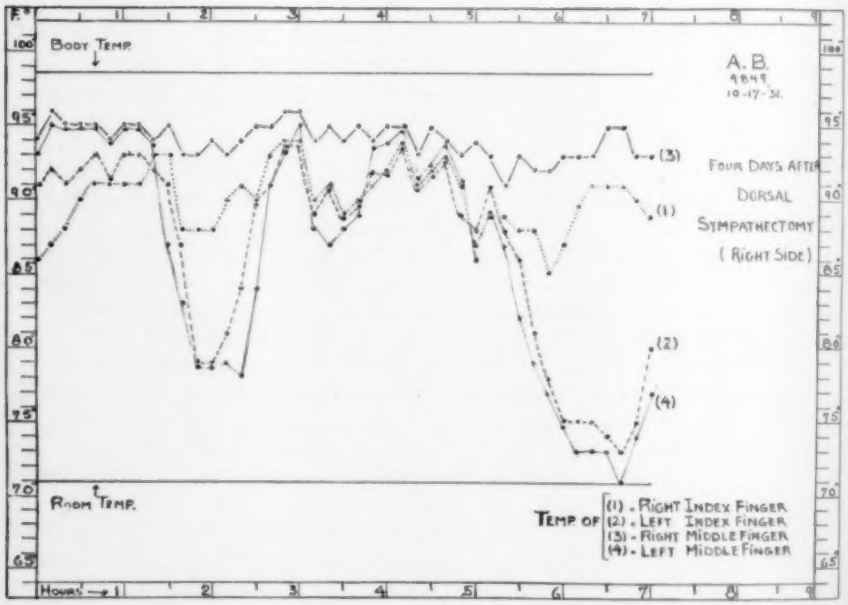

Chart III.

of the nails. Chart II shows the effect of paravertebral novocaine injection of the upper thoracic ganglia.

Dorsal Sympathectomy.—October 13, 1931, avertin-novocaine anæsthesia. Through a transverse incision over the second rib posterior the thoracic sympathetic chain was exposed on the right and the stellate ganglion and the trunk as far down as and including the second thoracic ganglion was removed.

Post-operative Notes.—The patient made an uneventful recovery and Chart III shows the temperature record of the extremities on the fourth post-operative day. There

FIG. 1.

was also marked subjective improvement. Figure 1 shows the areas over which there was complete absence of sweating indicating that the sympathectomy had been complete. It is interesting to note that this patient did not show a Horner's syndrome.

Lumbar Sympahectomy.—October 24, 1931, gas oxygen-ether anæsthesia. Through a left rectus incision the lumbar sympathetic trunk was exposed and a portion of it removed, including the second, third, fourth and fifth ganglia.

Post-operative Notes.—Following this operation he developed a mild pneumonic process which quickly cleared. There was marked subjective and objective improvement

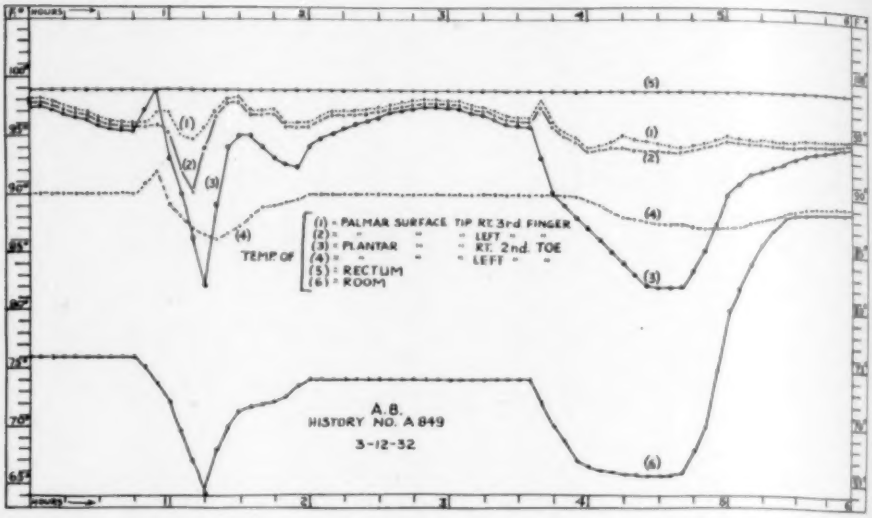

CHART IV.

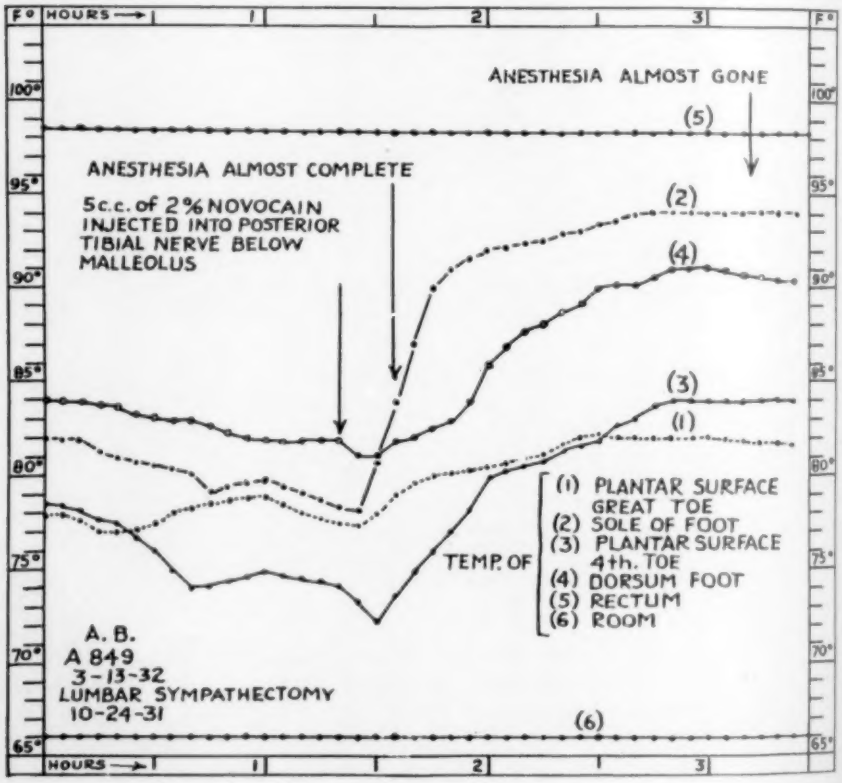

CHART V.

of the left foot and the pain in the left great toe disappeared. On washing the right hand in cold water three weeks after the dorsal sympathectomy there was distinct evidence of vasomotor spasm but of a mild degree. The patient was discharged home on November 7, 1931.

Interval Notes.—March 15, 1932. Since leaving the hospital he had gained twenty pounds, although he was still ten pounds under his maximum weight. There had been subjective and objective improvement in all extremities but particularly marked in the right arm and left leg. He had noted that the left hand still underwent marked color phases and occasionally on exposure to cold water he had noted slight color changes in the right hand. All ulcerative lesions had completely healed. There had been a marked increase in the rate of growth of the nails in the sympathectomized extremities particularly on the left foot, where it was necessary to cut the nails three to four times more often than on the right foot. He had noted no evidence of perspiration on the right

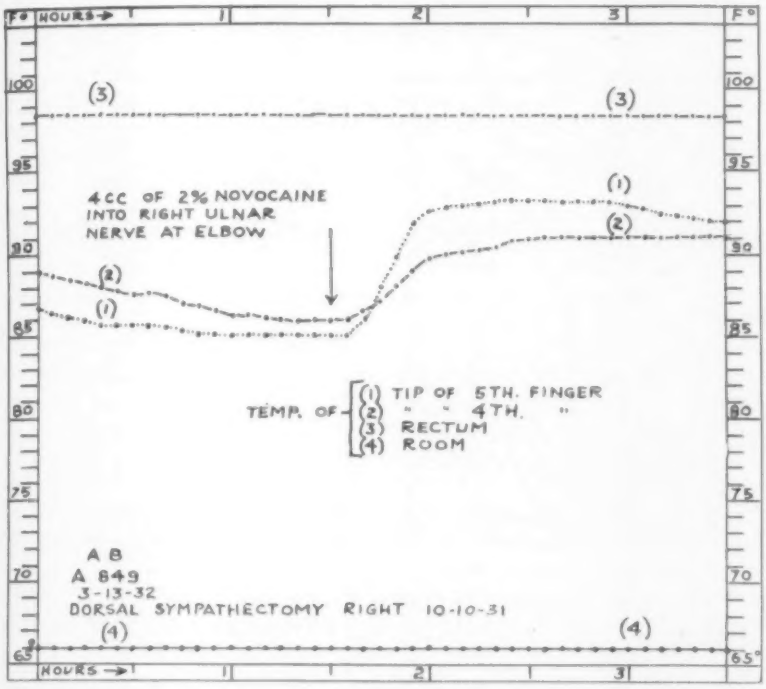

Chart VI.

hand but had occasionally noted one spot of perspiration on the sole of the left foot. There was a marked subjective feeling of warmth in the right hand and left foot.

Comment on Temperature Studies.—March 15, 1932. The patient was placed in the constant-temperature room, and records were made of the temperatures of both upper and lower extremities. Chart IV shows the response of the temperature of the extremities to changes in room temperature. In general there was a tendency for the right hand and the left foot to remain at a higher temperature as a result of the interruption of the sympathetic fibres to these extremities. This was particularly noticeable when there was a rapid change of environmental temperature demonstrating a greater range of temperature variation in the normal limbs. It was furthermore found that if the extremities were exposed to a lower room temperature (that is, 65° to 70°), there was a slow fall of temperature of the sympathectomized limb. After the temperature of the left foot had reached a low level, the left posterior tibial nerve was injected with novo-

caine just below the malleolus, and, as shown in Chart V, there was an immediate rapid rise in the temperature of the foot accompanied by subjective and objective evidence of vasodilatation. There was some difficulty in demonstrating this phenomenon in the right hand, and the temperature changes were never as great. However, they were likewise present. (Chart VI.) These findings suggest that there are still vasomotor fibres intact in the peripheral nerve to the extremities and that when these are blocked with novocaine that there is a release of vasoconstriction, with the resulting rise in temperature in these extremities. Because of the extent of the operative procedures and the number of ganglia removed and because of the sweating reaction obtained after operation, it had been thought that the sympathetic vasomotor fibres in the extremities had been interrupted. The above findings suggest that there are sympathetic pathways which are not interrupted by the usual operative procedures, and it seemed desirable to further investigate this phenomenon by experimentation on laboratory animals.

OBSERVATIONS ON SYMPATHETIC VASOMOTOR PATHWAYS IN DOGS

It is not within the limits of this paper to completely review the work which has been done in determining the course of sympathetic vasomotor fibres in laboratory animals, but rather merely to present a summary of the findings of some of our experiments, which will later be reported elsewhere in detail. Dogs were used in these experiments because of the fact that most of the previous investigations on the course of the vasomotor fibres have been carried out on this animal. In recent years the pathways by which sympathetic vasomotor fibres reach the peripheral blood-vessels after leaving the paravertebral chain have been carefully investigated. Since the work of the English anatomists and physiologists, namely Gaskell, Langley, Bayliss and Bradford, the levels at which the sympathetic vasomotor fibres leave the spinal cord and join the main sympathetic chain have been considered well-established facts. Langley carried out most of his investigation using the cat as a laboratory animal. The procedure by which he demonstrated the levels at which connector fibres left the spinal cord was to isolate the spinal roots and stimulate these at various levels; at the same time observing the appearance of sweat droplets on the footpad. He also used some animals having white footpads in which flushing as a result of vasodilatation could be observed. Gaskell used anatomical methods, and in the dog studied the distribution of the small medullated fibres in the anterior roots and the relation of their distribution at various levels to the presence of these fibres in the gray rami. Bayliss and Bradford, also using the dog as the experimental animal, studied the effect of stimulation of individual nerve roots as measured by the increase in size of the limb contained in a plethysmograph. These studies all indicated that the majority of the sympathetic vasomotor fibres left the spinal cord in the anterior root from the level of the first thoracic to the third or fourth lumbar vertebræ.

In the experiments carried out in this laboratory, the temperature changes in the feet were used as an index of the blood flow in the extremities. It was found that in dogs under amytal anæsthesia when the femoral artery was ligated below Poupart's ligament there was a fall in the temperature of the extremity. Following this if the spinal cord was transected in the thoracic region there was an immediate rise in the temperature of the extremity. It was also found that transection of the cord as low as the fifth or sixth lumbar vertebræ resulted in an immediate rise in the temperature of the foot as shown in Chart VII.

The work of previous investigators had shown that the majority of these fibres left the spinal cord between the level of the tenth thoracic and third lumbar vertebræ. Under the same conditions as previously stated it was found that if the spinal roots were sectioned extradurally from the level of the eleventh thoracic to the third lumbar, there might or might not be a rise in the temperature of the extremity. Following

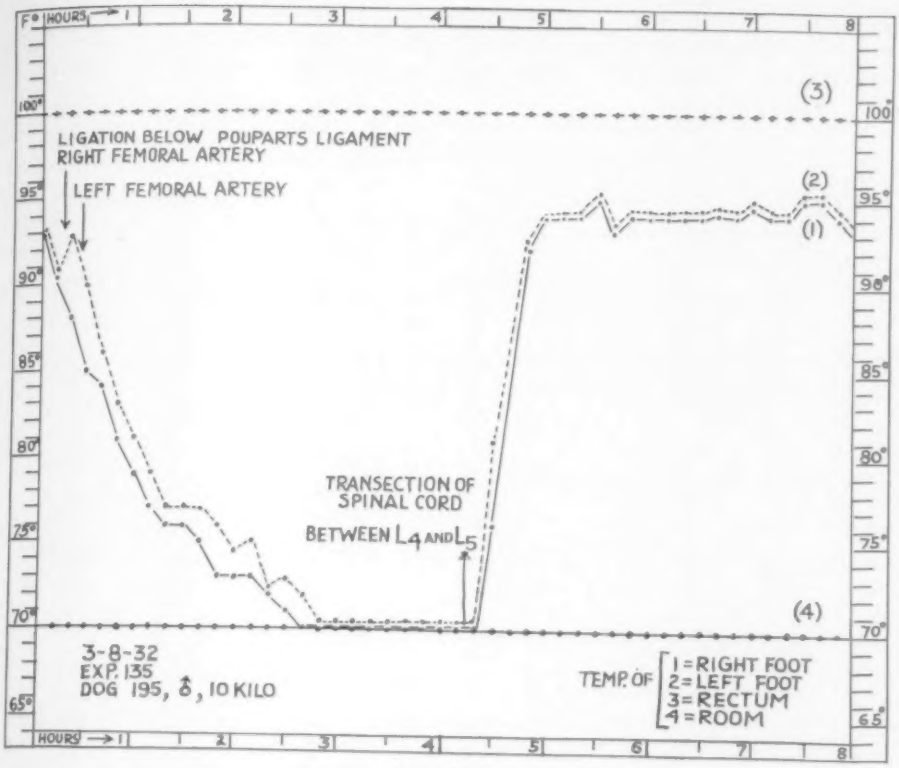

CHART VII.

this if the sciatic nerve was divided (Chart VIII) there resulted an immediate rise in the temperature of the extremity if none had previously taken place or an increase in the temperature when a previous rise had occurred. This indicated that there were

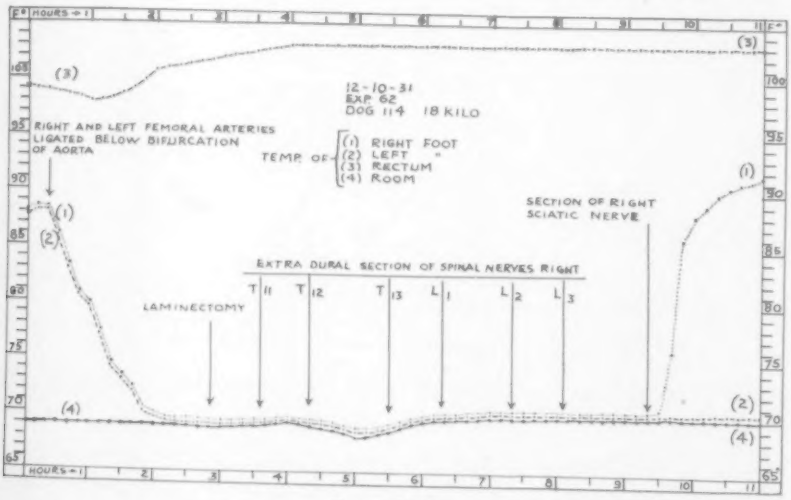

CHART VIII.

vasomotor fibres leaving the cord at levels other than between the eleventh thoracic and third lumbar. A third group of experiments was carried out in which the spinal roots

supplying the sciatic nerve only was sectioned, namely, from the fourth lumbar to the second sacral, and in these experiments also there resulted a rise in the temperature of the extremity. (Chart IX.) These experiments all suggest that there are vasomotor

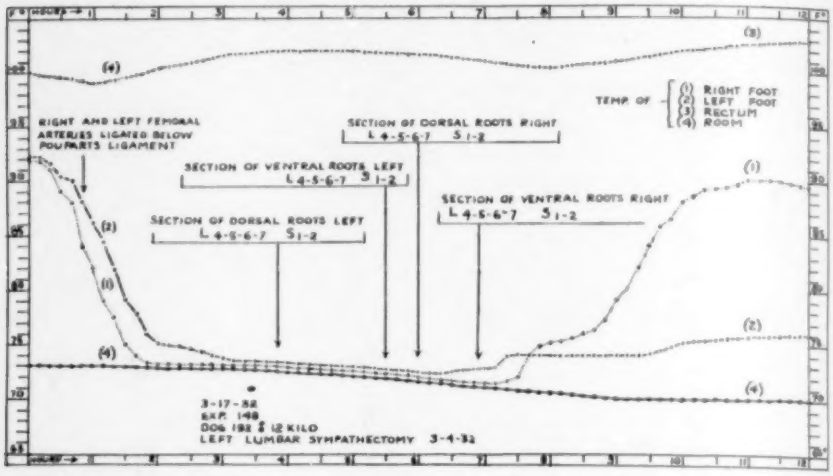
TEMP. OF (1) RIGHT FOOT (2) LEFT FOOT (3) RECTUM (4) ROOM
RIGHT AND LEFT FEMORAL ARTERIES LIGATED BELOW POUPARTS LIGAMENT
SECTION OF DORSAL ROOTS RIGHT L 4-5-6-7 S 1-2
SECTION OF VENTRAL ROOTS LEFT L 4-5-6-7 S 1-2
SECTION OF DORSAL ROOTS LEFT L 4-5-6-7 S 1-2
SECTION OF VENTRAL ROOTS RIGHT L 4-5-6-7 S 1-2
3-17-32
EXP. 148
DOG 182 ♂ 12 KILO
LEFT LUMBAR SYMPATHECTOMY 3-4-32

CHART IX.

connector fibres leaving the spinal cord at lower levels than have previously been assumed.

In addition, another group of experiments was designed to study the effect of removing the lumbar sympathetic chain in dogs. (Chart X.) In these experiments the sympathetic chain was extirpated from the level of the second lumbar vertebra to the level of the third or fourth sacral vertebra. Following this there was an immediate

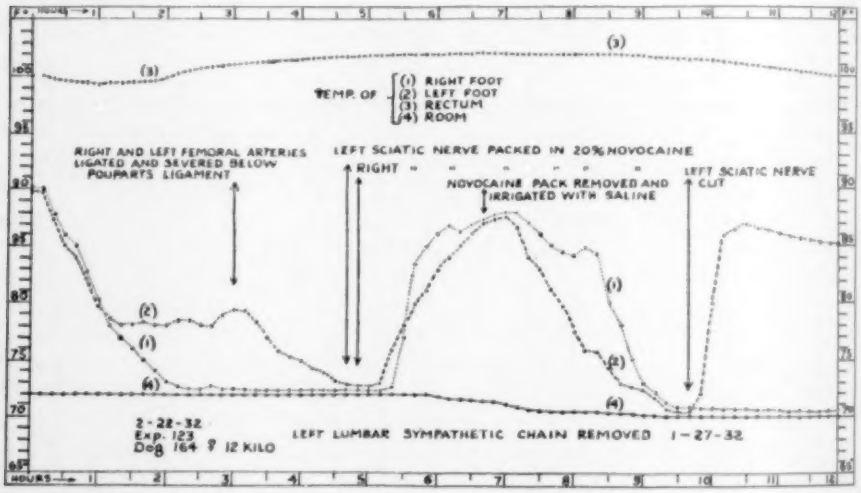
TEMP. OF (1) RIGHT FOOT (2) LEFT FOOT (3) RECTUM (4) ROOM
RIGHT AND LEFT FEMORAL ARTERIES LIGATED AND SEVERED BELOW POUPARTS LIGAMENT
LEFT SCIATIC NERVE PACKED IN 20% NOVOCAINE
RIGHT " " " " " "
NOVOCAINE PACK REMOVED AND IRRIGATED WITH SALINE
LEFT SCIATIC NERVE CUT
2-28-32
EXP. 123
DOG 164 ♀ 12 KILO
LEFT LUMBAR SYMPATHETIC CHAIN REMOVED 1-27-32

CHART X.

vasodilatation. Temperature studies were carried out over a period of weeks, and in general it was found that this vasodilatation became less and less marked until at a period from two to six weeks following operation the temperature of the sympathectomized limb, when the animal was kept in a constant environment of 70°, was essentially the same as the normal limb. If the sciatic nerve was then packed in novocaine or

sectioned, there was an immediate rise in the temperature of the extremity. In some dogs even at the end of two months there was still a considerable vasodilatation in the sympathectomized limb. In all of the dogs the difference in the two limbs could be demonstrated by differences in response to exercise or rapid temperature changes. Also the degree of response after section of the sciatic nerve varied considerably.

At present we are unable to interpret these findings but they suggest that possibly there are sympathetic vasomotor pathways which do not pass through the paravertebral ganglionic chain.

Summary.—(1) The varied results obtained by operative procedures designed to interrupt sympathetic vasomotor pathways may in part be explained by our lack of knowledge of the exact course pursued by these fibres and particularly the levels at which they leave the spinal cord.

(2) Evidence has been presented which suggests that the connector fibres between the spinal cord and sympathetic chain have much wider distribution than has formerly been supposed.

(3) In view of this fact, it is suggested that operations designed to remove a portion of the sympathetic ganglionic chain should be made even more extensive and particularly in lumbar sympathectomy, the ganglia should be removed to as low as the level of the second sacral vertebra.

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THE QUANTITATIVE DETERMINATION OF VASOCONSTRICTOR SPASM AS A BASIS FOR THERAPY IN PERIPHERAL ARTERIAL DISEASES *

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AND

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The realization that spasm plays a part in a considerable proportion of the common peripheral arterial diseases made it necessary to develop methods for measuring it. The first attempts were naturally concerned more with the demonstration that vasoconstriction was or was not present in any given case under study. These qualitative tests had a definite place in emphasizing to the profession the importance of spasm in the peripheral arterial diseases.[1, 2, 3, 4]

The methods generally adopted to bring out the presence or absence of spasm depend upon surface thermometry and tests which free the blood-vessels from the influence of sympathetic vasoconstriction. It was necessary first to develop a convenient and rapidly responding type of surface thermometer. It was also essential to recognize the factors which conditioned the application of this instrument. If the external physical factors could be kept relatively constant, then surface temperature would offer a means of gauging the volume and velocity of the blood flow through the cutaneous areas. All these conditions had been fulfilled by careful investigations in many laboratories.[5, 6]

It seemed to us to be of the first moment to establish proper normal controls and standards. Accordingly, our original investigations were made upon subjects with normal peripheral blood-vessels. Constant environmental conditions were established and tests gradually evolved which allowed us to record the response of the normal vessels when released from the influence of the sympathetic vasoconstrictors. In this way, the *normal vasodilatation level* was defined. It was recorded as the maximum surface temperatures attained when all sympathetic vasoconstriction had been removed by appropriate measures in the area tested.[7]

The most convenient method for testing that we have found is by conduction nerve block.[8, 9] The level for conduction block anæsthesia is 30.5° C. (89.9° F.) at a room temperature of 20° C. (68° F.). The importance of establishing the vasodilatation level is apparent. Without it, we have no normal base line or control. With it, we have a mathematically significant figure, so that quantitative estimations are possible, in comparing the response

* Expenses of this investigation were defrayed by a grant from the Fluid Research Fund of the Rockefeller Foundation.

of diseased arteries to that of normal ones. The precautions necessary for obtaining these data have been described in several previous communications.[8, 9, 10]

The whole problem of diagnosis of peripheral arterial disease resolves itself into a few relatively simple rules and procedures. In the first place, it is necessary to determine whether the complaint is due to a failure of the blood supply. This can be determined by the history and the ordinary methods of physical examination. The signs and symptoms produced by a failing blood supply are those due to ischæmia of the skin or muscles. There will consequently be color changes of pallor, rubor or cyanosis; tinglings, paræsthesias and actual pain; fatigue, cramps in the muscles and intermittent limping; atrophy or hypertrophy of the skin, nails and subcutaneous tissues; and, in late stages, patches of gangrene or complete circulatory failure to a part—massive gangrene.

The next problem is to decide whether the circulatory failure is due to organic occlusion of the main vessels, sympathetic vasoconstriction, or to a combination of the two. This requires special apparatus in the form of a rapidly responding surface thermometer; and a special test to abolish the influence of the sympathetic vasoconstrictors. The lower limits of the normal vasodilatation level serve as a control level which should be reached if the circulatory channels are not occluded. Having once determined that there is an abnormal function of the peripheral arterial vessels, by this test it is possible to decide whether the trouble is due to occlusion, spasm or both. If under these circumstances on paralyzing the sympathetic vasoconstrictors the surface temperatures rise to the normal vasodilatation level, the condition is obviously due only to spasm. If there is little or no rise, the condition is predominantly one of occlusion; and when mixed, the relative proportions of spasm and occlusion can be determined by subtracting the maximum surface temperature rise from the normal vasodilatation level. The number of degrees by which there is failure to reach the normal vasodilatation level is the occlusion index.

Raynaud's disease in its more severe forms appears to offer an exception to this test for distinguishing arterial spasm and occlusion. There is probably a dual control of the spasm in these instances—a local spasm expressed as hypersensitiveness to cold—and the central vasoconstriction.[11] Fortunately, these cases offer no difficulty in the application of the test to the common vascular diseases, as the diagnosis in them is easily made by the character of the attacks when they are severe enough to fail to respond to nerve block. The spasm can also be readily abolished under these circumstances by the application of heat.

The following cases will serve to illustrate the value of quantitative preoperative determinations of vasoconstrictor spasm in individuals with peripheral vascular disease. There is often a problem of surgical judgment even when it is clearly demonstrated that spasm is an important element in the circulatory failure.

CASE I.—F. G., No. 46101, a man, fifty-four years of age, was seen because he had attacks of intermittent claudication on walking. For several months he had noticed mild pain and cramping in the calves, especially on the right side. This was most prominent when he was exercising or going upgrade. The pain on the right extended as far as the hip and groin at times. Otherwise there were no symptoms. He usually smoked about thirty to forty cigarettes a day. Examination showed an exceptionally well-developed man. The positive findings centred on the peripheral vascular system. The brachial blood-pressure was 124 systolic, 72 diastolic. There were no signs of sclerosis in the vessels though the walls could be palpated. The right foot and ankle were cooler than the left. The right dorsalis pedis and posterior tibial arteries could not be palpated. Even the right femoral and popliteal arteries gave only slight pulsations.

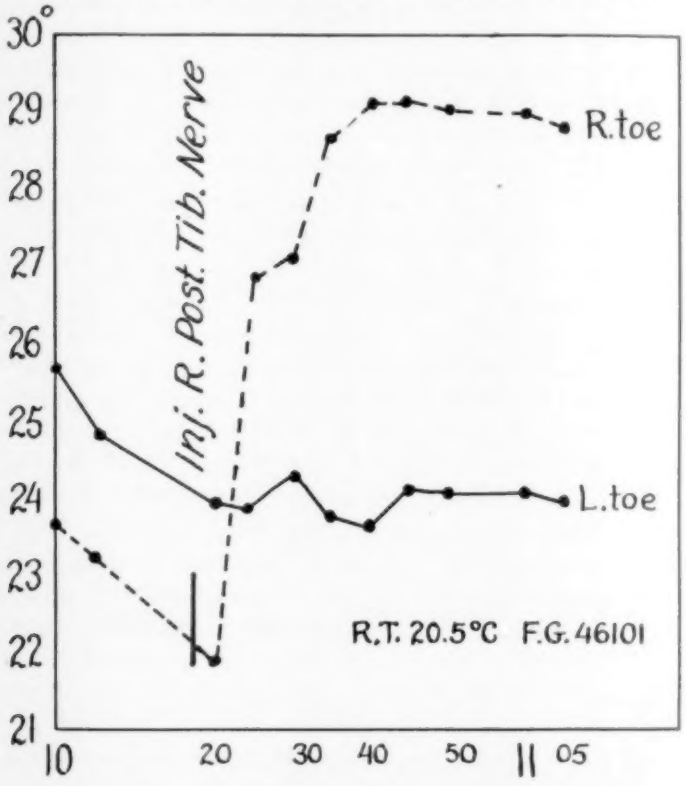

FIG. 1.—(Case I.) Nerve-block anæsthesia demonstrates that the vascular insufficiency is partly due to occlusion but mainly to spasm. The occlusion index is 1.5° C. Lumbar ganglionectomy would undoubtedly improve the circulation in the right foot but the complaint was too slight for the major operation.

Pulsations could easily be made out in all the major arteries of the left lower limb. Röntgen-ray examination of the lower limbs showed no definite evidence of calcification of the arteries. When the right posterior tibial nerve was injected with 1 per cent. procaine, the surface temperatures in the anæsthetic areas showed a prompt rise to 29° C. This indicated an "occlusion index" of 1.5° C. and the presence of a large element of spasm. (Fig. 1.)

The symptoms in this patient were of moderate degree. He could get about for his usual activities without embarrassment. The cramps were brought out only by exceptional activity. Should he be subjected to the

risk of a major operation? Undoubtedly, the peripheral circulation would be improved by such a procedure. The risk of the operation in such a patient should be carefully weighed against the benefit to be obtained. We decided, in this instance, that the symptoms were not sufficiently grave to warrant the procedure. This patient might conceivably go for years without being incapacitated. This type of case makes the surgeon wish that a less extensive operation were available.

The next patient, on the other hand, although urgently in need of relief, presented the opposite picture. Spasm seemed to be largely responsible for his severe claudication. There were many complications, however, which made the ideal treatment too hazardous to be considered.

Case II.—G. S., No. 52560, a man of seventy years, was admitted to the medical service because of attacks of angina pectoris. In addition he complained of painful cramps in the left leg and foot. Eleven years ago there was a temporary paralysis of one arm. This cleared up rapidly and there were no other symptoms. There had been a non-productive, hacking cough for five years. Four years ago he began to suffer with attacks of paroxysmal tachycardia. These attacks were controlled by pressure over the vagus. Five months ago, there was an attack of difficult breathing and weak, irregular pulse. Digitalis was prescribed. Two months later he had his first attack of anginal pain. There was a sensation of precordial pressure with radiation of pain down both arms. Similar attacks have recurred since, all relieved by nitroglycerine. Three weeks before admission the patient was found unconscious by his wife. He was cold and sweating and had a weak irregular pulse. It was an hour before warmth could be restored to his body. He did not recall the episode on waking, and had a "thick tongue" for some time. He also showed a memory defect as information had to be repeated several times before he understood it. This period passed after a little while and he apparently recovered completely. The painful cramps in the left leg began two years ago. They came only at night, not when he was up on his feet. They started in the second and third toes which flexed under in definite spasms; and spread across the flexor muscles of the foot and up into the calf. The attacks were very frequent and painful with short periods of intermission. They had been relieved by forcible hyperextension of the affected toes; or by hanging the foot over the edge of the bed. Rarely during the two years had he been free from these nightly attacks of cramping. They had often been associated with precordial anginal pain as well. There had been nocturia, once or twice for the last fifteen years. The patient had always been nervous and highstrung and this seemed to aggravate his condition, according to his wife. He appeared on examination to be a senile man who had evidently suffered considerably in recent months. There were râles at both bases posteriorly and an impaired resonance over the whole back. The heart was not enlarged nor irregular in action but an electrocardiogram indicated myocardial damage and right ventricular preponderance. The blood-pressure was only 140 systolic and 80 diastolic. There were no evidences of peripheral arteriosclerosis either by physical examination or by Röntgen-ray studies. The prostate was definitely enlarged with benign hypertrophy of the right lobe. The left posterior tibial nerve was anæsthetized with 1 per cent. procaine. There was a fairly rapid rise in the surface temperatures in the anæsthetic area to the normal vasodilatation level. This indicated that without doubt the major portion of his peripheral vascular complaints was due to overstimulation of the sympathetic vasoconstrictor fibres. (Fig. 2.)

In this old man, with his poor general condition, a left lumbar sympathectomy, although it might give definite relief, would carry a very great

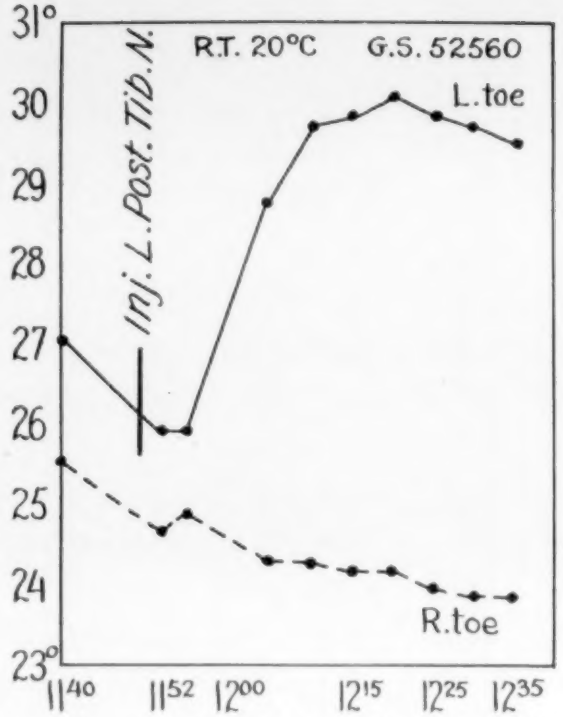

FIG. 2.—(Case II.) The nerve block clearly indicates that the major part of this vascular disease is due to spasm. The rise is to within 0.5° C. of the normal vasodilatation level.

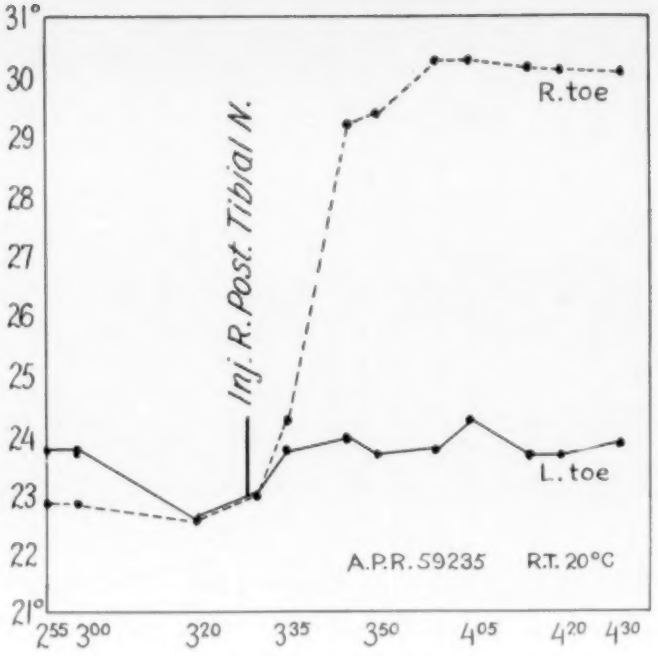

FIG. 3.—(Case III.) Nerve block is followed by a rise in surface temperatures to the normal vasodilatation level. This indicates that spasm is responsible for the vascular deficiency in this case.

risk. In fact, it was considered better judgment to perform no operation in his case. The dangers of myocardial failure, bladder obstruction, hypostatic pneumonia and intracranial hæmorrhage were all only too apparent.

This next patient seemed to be in good general physical condition. His trouble was progressing rapidly, so that he feared total incapacity for carrying on his occupation. The whole situation was frankly discussed with him, and the risks of operation presented. We felt that operation would probably bring him relief. This is one of the border-line cases in which it is extremely difficult to be certain as to the best treatment.

Case III.—A. R., No. 59235, a man of fifty-nine years, was seen because of increasing claudication in the right leg. He had never had any trouble walking till four months ago. Then he noted a pain in the calf of the right leg when he walked very far. This pain had become more persistent until now he cannot walk a short city block without difficulty. He had always smoked a goodly amount—at least a package of cigarettes a day and frequently one or two cigars as well. On examination the feet were of normal color. There were good pulsations in the left posterior tibial and dorsalis pedis arteries but no pulsation could be determined in the right posterior tibial. The right dorsalis pedis pulsation was present but diminished. Röntgen-ray examination showed slight beading with calcification of the right anterior tibial artery and some calcification over the left popliteal artery. There was very definite calcification in the left dorsalis pedis and posterior tibial arteries. The arteries on the left side seemed to show more calcification than on the right side where the symptoms were noted. Injection of the right posterior tibial nerve with 1 per cent. procaine caused a rise in the surface temperatures to the normal vasodilatation level. It is apparent from this test that there was a marked element of spasm in this picture. (Fig. 3.)

That operation is not without danger is attested by the record of the following patient. He was considered to be urgently in need of operation to preserve a failing circulation. The reaction to the operation was decidedly severe. For almost one week it was doubtful whether he would live. His condition then improved and he was discharged after a slow convalescence. The circulation has improved, but though he has not had claudication in the right leg, there have been small areas of migratory phlebitis.

Case IV.—C. B., No. 24437, a Jewish man of fifty-one years, was admitted to the hospital in May, 1929. He had been troubled with pain in the calf muscles of the legs for ten years. This pain came on after walking. It had been getting progressively worse during the last two years until now he cannot walk more than 100 feet. The pain, in the nature of a muscle cramp, never came when the patient was at rest. It practically disappeared as soon as he stopped walking. He was an obese, emphysematous type. The heart was not enlarged. The blood-pressure was 164 systolic, 88 diastolic. There was an absence of pulsations in the vessels of the feet and in the popliteal arteries on both sides. The femoral pulsations were easily felt, the right being weaker than the left. When the feet were elevated there was a cadaveric hue and in the dependent position both feet were greatly congested. The tip of the great toe and the second toe of the right foot were a purplish black, much more congested than any other part of the foot. There was no calcification of the arteries by Röntgen-ray. A diagnosis of thromboangiitis obliterans was made. A right lumbar sympathetic ganglionectomy was done through the abdominal approach a few days after admission. Convalescence was stormy and complicated by acute dilatation of the stomach, paralytic ileus, and broncho-

pneumonia. After a critical period of about one week he gradually improved and was discharged about one month after entry.

There was obviously some improvement in the circulation of the right leg following operation, as the surface temperatures were distinctly higher than those on the left. The response was almost to the normal vasodilatation level on the right side. Since operation the function of the right leg has improved, while that of the left leg has become more impaired. He can now walk as far as a quarter of a mile without getting symptoms on the operated side. Claudication is then present on the unoperated side which limits his activity. There is a considerable variation in the condition, at times he is much better than at others. He has had two small areas of tenderness in the right calf which probably represent migratory phlebitis. The right foot remains warm and dry in decided contrast to the cold, damp, cyanosed left extremity. The surface temperature on the right great toe is consistently at 29° C. to 30° C., whereas on the left great toe it is 23° C. to 24° C.

The value of the pre-operative quantitative determinations is well illustrated by this next patient, who gives the average result to be expected after operation. It is usually possible to be certain that the post-operative result will closely correspond to the pre-operative quantitative determination. This has been our experience in the great majority of instances. The post-operative surface temperatures usually record a little higher than the pre-operative nerve-block test, which is to be expected. In working out the nerve-block test we found that it did not give quite as high surface temperature readings as those following spinal or general anæsthesia.

Case V.—N. C., No. 53908, a Russian Jew, forty-eight years of age, was admitted to the Strong Memorial Hospital in January, 1932. He had been in the hospital a few months previously because of chronic bronchitis, asthma, chronic tonsillitis, and sinusitis. These ailments had followed an attack of typhoid and pneumonia thirty years previously. While he was on the medical service he stated that he had had pain in the calf muscles of the right leg and pain along the right shin bone when he walked about two blocks. He also claimed that his feet became quite cold at times. There had been pain at night in this leg also, and a sense of tiredness in it on exertion.

Examination revealed that the feet were cold and bathed in perspiration. There was no pulsation of the right dorsalis pedis artery made out although the left one had an excellent pulse. Pulsations could be easily demonstrated in the other arteries of the limbs. When the patient was nervous or was in a cold room the right great toe became markedly cyanosed.

When both feet were elevated and the toes exercised, the right great toe showed a cadaveric color. When the feet were dependent there was a cyanosis of this same digit.

Röntgen-rays showed no definite calcification in the walls of the right dorsalis pedis artery but possibly a little evidence of sclerotic changes in the posterior tibial artery.

Examination was negative for diabetes and syphilis.

The right posterior tibial nerve was injected with 1 per cent. novocaine. There was a rapid rise in the temperature in the toes and sole to the normal vasodilatation level. This was interpreted to mean that the circulatory deficiency was on a vasoconstrictor spasm basis. Sympathectomy was advised but refused.

He was discharged from the hospital but when he began to resume his activities he also had trouble in his left leg. Both feet were cold a greater part of the time. The cramps and pains continued if he walked for any distance. He noticed that his toes had a purplish color when the feet hung down. Just above the left ankle, the leg became hot and swollen. He felt a weakness in both legs. He reëntered the hospital

for operation. The only new finding on examination was a reddened area about six centimetres long just above the ankle on the medial aspect of the left lower leg.

A diagnosis of thrombo-angiitis obliterans was made. Right lumbar ganglionectomy was performed through the abdominal approach. The patient had considerable cough following operation but his course was in general satisfactory. There was a decided improvement in the color, warmth and comfort of the right leg immediately following operation. Surface-temperature readings taken about three weeks after operation showed a very close correspondence with the pre-operative quantitative determinations. (Fig. 4.)

In our experience it is not uncommon to find a gradual improvement in the surface-temperature readings as time goes on. This result is possibly to be expected in a good number of these patients. It must represent the opening of collateral channels. This may be an argument also for operation even when there is an occlusion index of several degrees. We have not had enough experience, however, to be certain of this point.

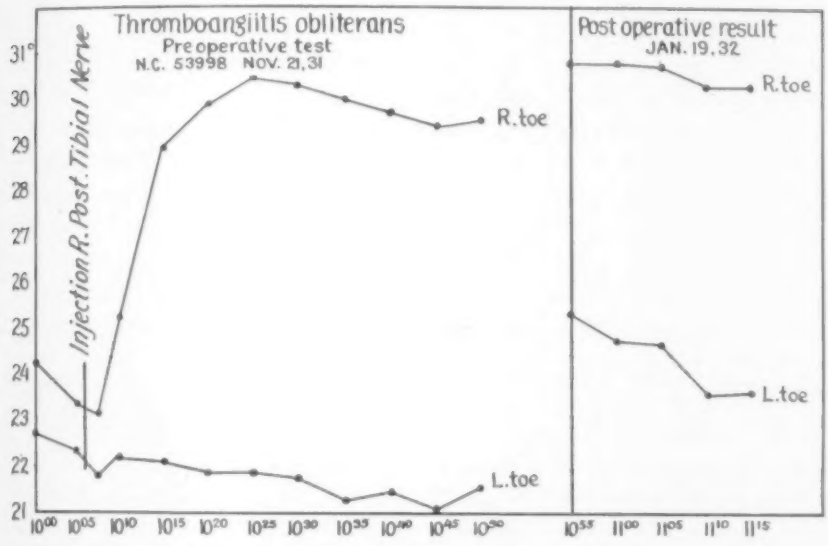

FIG. 4.—(Case V.) The post-operative determination checks almost exactly with the pre-operative quantitative text. This is the average result to be expected.

CASE VI.—P. B., No. 40711, a Russian Jew, thirty-one years of age, was admitted to the hospital on November 6, 1930, because of pain in the right foot. He first began to have sharp shooting pains in the toes of his right foot in September, 1929. The foot was icy cold and white at this time. The pain came on more often when he was on his feet and it continued to grow worse. In January, 1930, the right femoral vein was ligated in another city. The leg swelled up greatly following this and the foot became a dusky purple in color. The pain, however, was relieved until four to five days prior to entry. He was a well-developed man. The main interest in the examination was in the lower extremities. There was marked swelling of the toes and dorsum of the right foot. In the dependent position this foot became plum colored. There were bronzed streaks over some of the superficial veins indicating an old thrombophlebitic process. Both popliteal arteries gave good pulsations but on the right side only a very faint pulsation could be made out in the dorsalis pedis artery and no certain pulsation in the posterior tibial artery. The pulsation was excellent in the left posterior tibial artery and fair in the dorsalis pedis artery, though at times difficult to palpate.

A vasomotor test under nitrous oxide-ether anæsthesia gave evidence of a large element of spasm, the surface temperature rising to 30° on the right great toe in contrast to a rise to 32° on the left great toe. Röntgen-ray examination showed no evidence of calcification of the arteries. A diagnosis of thrombo-angiitis obliterans was made. Right lumbar ganglionectomy was done by the anterior intra-abdominal route.

The operation was well borne and the immediate effects on the circulation of the right foot were almost as prognosticated from the preliminary tests. The œdema and cyanosis were absent and the right foot remained of good color on discharge from the hospital. The surface-temperature readings on the right great toe one month after operation were 28° C. and 29° C. as against the readings of 23° C.–24° C. for the left big toe. The swelling was gone and the color better except in the dependent position, when it still assumed a purplish hue. Five months after operation he had a dull constant pain under the left great toe. The skin over this area was swollen, bluish and tender. Eleven months after operation his right foot remained warm, pink and dry, whereas the left foot was covered with perspiration, was several degrees colder and the toes were whiter than those on the right. There was also a slightly tender, subcutaneous mass on

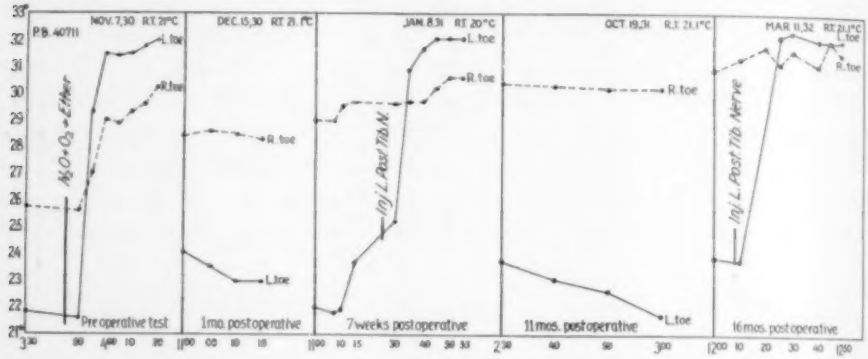

FIG. 5.—(Case VI.) The immediate result (one month following operation) did not appear to be as good as the pre-operative determination indicated. There has been a slow but steady improvement as time goes on. The big toe appears to have reëstablished an adequate circulation by the development of collateral circulation.

the right leg just above the ankle. This probably represented thrombosed veins, another evidence of migratory phlebitis still occurring even in the sympathectomized area. Sixteen months after operation the surface-temperature readings on the sympathectomized limb were at the normal vasodilatation level. There has been a slow but steady improvement in the surface temperatures over a long time. This seems to point to the establishment of better collateral circulation. (Fig. 5.)

An unusual but gratifying result is occasionally observed when there is an immediate post-operative improvement better than the quantitative pre-operative test would lead us to look for. This unexpected improvement occurs only in small patches and is not a general phenomenon over the whole denervated area. It must not be counted upon as there is no way to predict when it will occur. Fig. 6 shows the progressive improvement in two small areas. It brings out also very well that the initial temperature readings may be widely separated, varying in their height with uncontrollable psychic factors. The patient should be left exposed for at least an hour according to Benedict[6] in order for the surface temperatures to reach stability. This has not been practical but we have adopted a half-hour period at constant temperature conditions before making readings, in this way getting at least

the trend of the temperature curves. The first part of the chart shows that sympathetic vasoconstriction was prominent on both sides. The patient did not know what to expect. He had been told that he would have a test for his arteries. He was wheeled to the windowless, constant-temperature room where his feet were exposed for one hour. During this time the temperatures progressively dropped (not shown in the chart) probably through psychic upset in regard to what was in store for him. When the nerve had been injected there was a good anæsthesia obtained over its whole distribution and in other areas tested vasoconstriction was almost abolished, the surface temperatures reaching 29° C. to 30° C. These areas are not included in the chart in order to simplify its interpretation. The fact that anæsthesia was obtained and that other areas showed release from vasoconstriction should dispose of the possible objection that the test was inadequate. In the second part of this figure, the patient knew what it meant to have readings done. It was with a different outlook that he approached this trial and he displayed in consequence little vasoconstriction even on the unoperated side. The improvement in surface-temperature readings in the two small areas was decided. It can best be judged by the nearness to the vasodilatation level, 30.5° C., and not by the relation to the starting point. This is the importance and significant reading. The other areas on the operated side recorded temperatures almost identical with the pre-operative quantitative determinations. The third part of the chart shows a still greater improvement and a wider separation between the readings on the operated and unoperated sides. The toe and sole on the operated side now come into the limits of the vasodilatation level. This can only mean a reëstablishment of collateral circulation or a canalization of the occluded main vessels, more likely the former.

Case VII.—W. R., No. 56630, a Russian Jew, fifty-six years of age, was admitted to the Strong Memorial Hospital on January 21, 1932. One year ago he began to have pain in his left great toe. This toe became inflamed and in three weeks it assumed a brownish-black color. He went to a hospital where he was put to bed for about eight weeks during which time the toe gradually lost some of its blackness. He then began to experience a dull continuous pain in his left heel and arch; and after that pain of the same general character in his left thigh. He had spent a great deal of his time in bed since this experience as he was much afraid of aggravating the condition. He had always been a heavy smoker. He had upon examination a chronic bronchitis and no other abnormalities except for his local condition. There was an obvious disease of the arteries of the left leg. The toes on this side showed an atrophy of the subcutaneous tissues and a thinning of the skin. Just behind the medial surface of the left great toenail there was a small area where there had been an ulcerated lesion. The epithelium had not quite covered this area. In the dependent position of the left foot, there was rubor and upon elevation the toes became white after exercise. The left dorsalis pedis pulsation could be felt but it was very small. The posterior tibial pulsation was fair but of much smaller volume than the right posterior tibial pulsation. The left popliteal pulsation was not easily felt. All pulsations on the right were good except the dorsalis pedis, which was only fair. There was no calcification of the vessels by Röntgen-ray. There was no evidence of syphilis or diabetes.

Anæsthesia of the left posterior tibial nerve was carried out. It showed a good rise in the heel and sole and a delayed and incomplete rise in the toes. The temperature of the great toe reached only 26.5° C., an indication of a considerable degree of occlusion to the blood supply. A diagnosis of thrombo-angiitis obliterans was made. A left lumbar ganglionectomy was done by the anterior abdominal approach. The post-operative recovery was satisfactory. There was a decided improvement over the pre-operative determinations almost immediately following operation. The surface temperatures recorded within two weeks indicated a greater improvement than had been looked for in certain small areas—the great toe and parts of the sole. This could be explained only by the general improvement in the collateral circulation immediately adjacent to these areas and the opening up of new channels in the areas themselves.

Two months after operation the left foot was warmer than the right. (Fig. 6.) In the dependent position there was still decided rubor of the great toe. There was relief

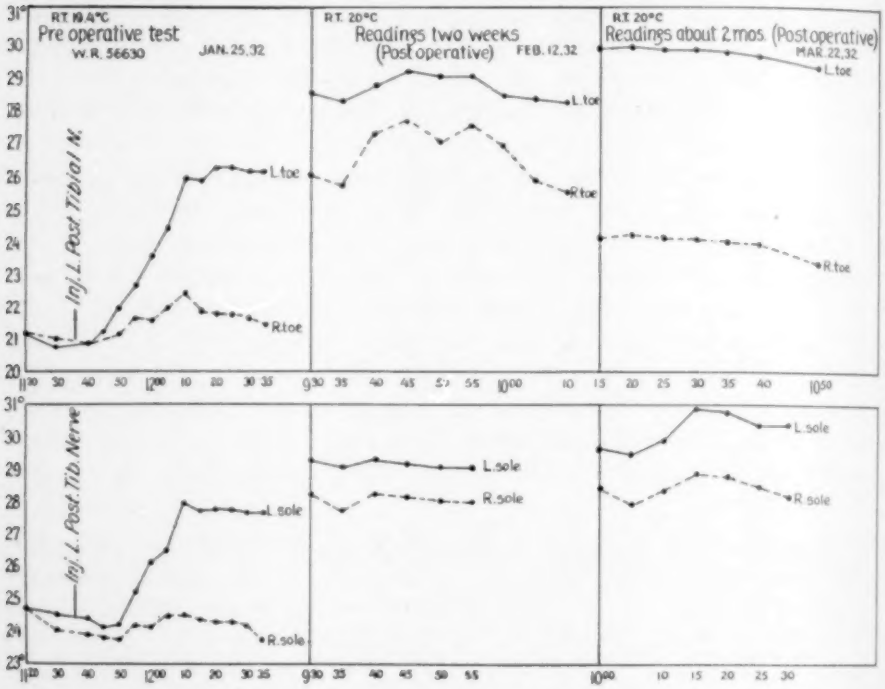

FIG. 6.—(Case VII.) This chart is more fully explained in the text. The records have been abbreviated to save space. There should be a thirty-minute control period before readings have any significance. These charts illustrate the importance of the vasodilatation level as compared to the rise from a starting point. The nearness to 30.5° C. is much more significant. There has been a rapid progressive improvement in small areas in this case.

from the burning pain in his toes, and the claudication in this limb had disappeared. Surface-temperature readings demonstrated a progressive improvement in the circulation through the subpapillary network. This collateral circulation had apparently responded to the removal of sympathetic influences and the surface temperatures were in the normal zone at the vasodilatation level. The left foot was in excellent condition four months after operation. The ulceration had completely healed and the foot was warm.

The importance of the collateral circulation in any type of peripheral ischæmia whether due to occlusion or spasm cannot be overemphasized. This has been recognized by the great master surgeons since the time of Hunter. Halsted and Matas repeatedly have called attention to the significance of

developing collaterals in diseases of the arteries. Treatment has been of benefit in proportion to the success in dilating these channels. Most of the measures advocated for relief of the peripheral arterial disorders have as their ultimate object the stimulation of a sufficient collateral network to keep the tissues viable. Lewis and Reichert,[12] recognizing this principle, went so far as to ligate the main arterial channels in thrombo-angiitis obliterans. Sympathetic ganglionectomy affords the most continuous permanent dilatation of the collateral circulation of any method yet proposed. The pre-operative quantitative tests which we have sponsored give a fairly accurate estimate of the results to be expected following removal of the sympathetic vasoconstrictors. The gradual general improvement with time, and the unusual immediate striking improvement in small areas in some cases, must be taken as indications of improved collateral circulation.

Conclusions.—In actual practice, the immediate results achieved by sympathectomy generally correspond quite accurately to the pre-operative quantitative determinations.

The immediate post-operative improvement in claudication is usually striking.

In some instances, the immediate post-operative results as measured by surface-temperature readings are better than the pre-operative determinations. This immediate improvement is usually confined to small areas and is not a widespread reaction.

Late post-operative results frequently demonstrate a slight general improvement in surface-temperature readings over the pre-operative determinations. This is undoubtedly dependent on an improved collateral circulation.

In thrombo-angiitis obliterans sympathetic ganglionectomy does not give assurance of freedom from a continuation of attacks of migratory phlebitis. In our series recurring phlebitis has been noted fairly often in the sympathectomized areas. These episodes are usually self-limited with spontaneous remission of acute symptoms. An occasional conservative amputation of a digit becomes necessary when gangrene supervenes. It is our impression that under these circumstances the local amputation can be carried out with more assurance that it will be successful, and that re-amputation will not be necessary. The improvement in collateral circulation to the adjacent areas following sympathectomy is probably responsible.

In any given case the actual or potential disability should be balanced against the risk and promise of the operation.

Both lumbar and cervical sympathectomy are major operative procedures which should not be undertaken without strong indications for their use.

In individuals beyond fifty years of age who complain of only slight degrees of claudication, and who exhibit neither severe pain nor impending gangrene, we advise against operation as being too radical.

In individuals with only occasional attacks of arterial spasm, relieved by heat, we believe that the risk of operation outweighs the disability. Conse-

quently, we are very conservative in operating on the usual examples of Raynaud's disease.

In dealing with the purely occlusive types of arterial disease, the treatment adopted in our clinic has been recently outlined by Pearse.[13]

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SURGICAL TREATMENT OF CERTAIN VASCULAR DISORDERS BY SYMPATHECTOMY

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It is becoming increasingly more evident that the clinical result in the treatment of Raynaud's disease by sympathectomy has not borne out the supposition that Raynaud's disease is due solely to spasm of the arterioles under the control of the sympathetic nerves. Claud Bernard's discoveries of the vasoconstrictor fibres in the sympathetic nerves have been proved. It has been proved also that sympathetic fibres are part of a mixed and sensory nerve. It is not now generally believed that the course of the sympathetic nerves runs any considerable distance in the walls of the vessels, not far enough at all events to be a factor in the consideration of these vascular diseases. Jaboulay, and later Leriche, exploited the periarterial vascular sympathectomy, and there are many cases recorded in the literature whose clinical results have been satisfactory following this procedure.

Braeucker[1] believes that: "Vasomotor tracts of the upper extremities have at the beginning the same course as the secretory tracts and reach the first thoracic and the inferior cervical ganglia. A row of fine branches goes from the ganglion to the subclavian artery and vein and wraps around the vessels forming a large irregular nerve plexus, and proceeding in their course with the blood-vessels. The largest mass of vasomotor fibres pass over the rami communicantes into the roots of the brachial plexus and run with it distally. From the spinal nerves small branches pass to the blood-vessels which enter the perivascular nerve plexus, increase and renew it, and carry this net formation to the periphery. The perivascular nerve plexus at the inferior cervical ganglion is formed from direct branches of the sympathetic, but the entire nerve plexus of the peripheral vascular structure is formed from indirect branches, from the sympathetic over the rami communicantes and the spinal nerves. The vasomotor fibres, therefore, enter the perivascular nerve net through two roots: (1) Direct, from the sympathetic; (2) indirect, from the sympathetic over the rami communicantes and the spinal nerves. The direct sympathetic branches form the perivascular net in the neighborhood of the sympathetic, and the indirect in all peripheral vascular areas, and the resulting plexus of both is continuous. The perivascular nerve net is a special apparatus which may live and function independent of the centres."

Foerster[2] reported a case of traumatic section of the brachial plexus distal to the rami communicantes. According to Langley, in the sectioned spinal nerve a degeneration of the spinal and vasomotor elements should have developed, but when he stimulated the digital artery there was severe pain. The nerve plexus of the distal vascular parts was not degenerated, although it was cut from its centre, and there was present an afferent tract in the perivascular net. The vascular net, therefore, remains intact after section of the rami communicantes.

That arteriospasm could be relieved by division of the appropriate sympathetic trunks: Kuntz,[3] in speaking of the sympathetic control of the vessels of the upper extremities, stated that complete sympathetic denervation of the upper extremity requires extirpation of the stellate ganglion and of the upper portion of the thoracic sympathetic trunk to the level below the communicating rami of the second thoracic nerve, or section

of the second thoracic nerve and peripheral rami arising from the thoracic sympathetic trunk above this level, in addition to section of the gray rami connecting the stellate and middle cervical ganglion with the brachial plexus.

Adson and Brown[4] state: "The strikingly maintained and unequivocable therapeutic effects of the lumbar and dorsal sympathetic ganglionectomy in Raynaud's disease seem to warrant the belief that surgical control in this disease is an accomplished fact."

Davis and Kanavel[5] describe a case of a patient who had Raynaud's disease. A right cervical sympathetic chain was removed. There was a prompt improvement in the right upper extremity. Within nine days immersion of the hands in cold water produced shortly afterwards a characteristic change.

Adson and Brown speak of failures in the upper extremities following cervical sympathectomy, but are expectant that division below the second thoracic ganglion would, according to Kuntz's theory, relieve spasm in the distal artery.

Lewis[6] believes an essential factor is present in the peripheral vessel. He finds also that in cases of cervical sympathectomy, digital arteries are expanded by warmth and constricted by cold when innervation has been lost. He says that spasm of the digital vessels may be produced in Raynaud's disease by local cold after division of the sympathetic cord below the second dorsal ganglion and extirpation of this and the inferior cervical ganglion. *The spasm of the vessels in this malady is not due to abnormal vasomotor impulse.*

Morton and Scott[7] say: *"The essential defect is a hypersensitiveness of the peripheral vessels to cold.* But the vasoconstrictor influences are powerful in bringing on and keeping up attacks, and their removal may be effective in prevention.

Spurling[8] reports that three typical cases of Raynaud's disease treated by sympathetic ganglionectomy had relief in the upper extremities, but for a period of six to eight months only. *In one case, a combination of trunk resection plus periarterial sympathectomy of the axillary artery* failed to effect a cure.

In a case reported by the writer,[9] about seven months after bilateral excision of the second thoracic and stellate ganglia, the result seemed all that was to be desired. The immediate improvement in color, increase in temperature and dryness of the skin, together with the very rapid disappearance of the beginning ulceration of the tips of two fingers made it obvious that the blood supply was materially improved; and over a period of months, during which warm weather came, the patient had no further experiences of the symptoms present prior to the operation. With the return of cold weather, and following an upset due to an experience of sudden alarm and fear, she again displayed characteristic symptoms, and during the ensuing winter her disease was definitely marked. She has been able to follow steady employment as a typist, but exposures of her hands to cold have caused her typical attacks. The immersion of her hands into water of 60° F. would be followed in a period of five to ten minutes by the characteristic changes. She states that sudden fear will cause her hands to change at once to a deep plum color. Physical influences, as cold to the hands, produce in her all the symptoms of an attack.

The lower extremities of this patient were greatly improved by lumbar ganglionectomies, done ten days after the cervical ones, and have remained well, being dry, warm and of a good color, without any local attacks during the entire winter.

It may be argued that the ganglia removed did not remove all the sympathetic fibres to the brachial plexus or that there is some other route of the fibres. The fact does, however, remain that by no method have severe cases of Raynaud's disease in the upper extremity been cured by the removal of sympathetic ganglia or nerves. Sympathectomies of a trunk ganglion or periarterial net do invariably produce some improvement, generally a dramatic one. But a return of symptoms after a period of months makes

it appear that there is either an unknown course of vasoconstrictor nerves or an inherent property of peripheral vessels to contract to the irritation of appropriate stimuli. If it is the latter it is difficult to explain why patients should be well and free of attacks for months following sympathectomy, nor does it help us to understand the invariable good results on the lower extremities following lumbar ganglionectomy.

Thrombo-angiitis Obliterans.—The treatment of this disease has in the past been uniformly unsuccessful in preventing, in certain cases, a progressive gangrene. In other cases there has been an arrest of the disease after a marked progression has been made. The severe cases have eventually come to amputation. Nothing surgery has had to offer has seemed of any real hope in arresting the disease.

In this disease there is a tremendously wide field for the application of surgery of the sympathetic nervous system. One may in any particular case test out by some suitable method the improvement in circulation following the temporary paralyzing of the vasomotor fibres going to an extremity. Those cases that are clinically well advanced, having a marked degree of phlebitis, do not react well with an increased circulation following either tests or operation. Early cases of this disease, however, do in nearly every instance show marked response to interference with the vasoconstrictor impulses. While this disease is in so far as is known a primary fault in the vessel wall, yet there is in every case a variable element of spasm, and during the time when important peripheral vessels are obstructed, or nearly so, an increase in the calibre of the vessels concerned in the compensatory circulation is of great natural benefit. A sympathectomy in thrombo-angiitis obliterans, in addition to increasing the blood supply and drying the limb by paralyzing the sweat glands, relieves the pain. This is an outstanding feature following operation. Whether the pain is relieved as the result of release of the vessel spasm or from a direct increased blood supply and the relief of an ischæmia it is impossible to say. Spasm of veins, as is sometimes experienced in recipients of transfusions, is a most painful experience. In Toronto a large number of cases of thrombo-angiitis obliterans have been treated by sympathectomy and as a result it is fair to say that the subjects have been well satisfied. The pain is often completely cured and pulsations that were formerly absent are found in many cases to have returned. Clinically one would think that cold was almost as great a factor in producing attacks in this disease as in Raynaud's disease.

Arteriosclerosis.—A condition such as arteriosclerosis is by no means limited to a certain part or extremity. It occurs in a person who is aging or aged and as it advances is found in some instances to involve the vessels of an extremity to such an extent that the circulation is seriously impaired. This type of case is in certain individuals amenable to treatment by lumbar sympathectomy. Testing of the case will give an idea as to the degree of vascular improvement consequent upon the cutting off of the sympathetic influence. It will be found to produce some effect and in cases of the disease

that are not too far advanced to have already serious reduction in blood supply to the foot a sympathectomy will be a satisfactory proceeding. In a case reported by the writer, a year and a half have elapsed since his operation, prior to which he was confined to bed for pain and impending gangrene of his feet. He was seventy years of age. Following a double lumbar sympathectomy no more opiate was administered. The pain left entirely and the blood supply increased to an obvious degree. He has resumed his normal life and continues well.

Sympathectomies have become a very common operation in Toronto, and it may be said in this connection that, of the 200 reported from three hospitals, there have been no immediate fatalities. Those that have occurred, two in number, were in persons markedly debilitated. In persons in fair health the operation is singularly free from any shock or untoward complications.

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RAYNAUD'S DISEASE, THROMBO-ANGIITIS OBLITERANS AND SCLERODERMA: SELECTION OF CASES FOR AND RESULTS OF SYMPATHETIC GANGLIONECTOMY AND TRUNK RESECTION

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The etiology of numerous diseases is becoming known as knowledge increases concerning the anatomy and physiology of the autonomic nervous system.[26] The altered function of this nervous system is not only responsible for certain diseases but undoubtedly determines the course of many other diseases since it influences blood flow, smooth muscle activity, glandular activity and carries afferent pain fibres.

Progress has been made in performing sympathectomy in cases of angina pectoris, congenital hypertrophic dilatation of the colon, cord bladder, spastic trophic and painful lesions of the extremities, and in selected cases of arthritis. The most satisfactory results have been accomplished by sympathetic ganglionectomy and trunk resection in the treatment of peripheral vascular diseases such as Raynaud's disease, thrombo-angiitis obliterans with vasomotor spasm of the collateral and nonoccluded arteries and acral scleroderma following Raynaud's disease. This study will contain a review of our experiences in the treatment of peripheral vascular diseases by sympathetic ganglionectomy and trunk resection.

Anatomy.—The sympathetic nervous system is an aggregation of ganglia, nerves, and plexuses through which the viscera, glands, heart, blood-vessels, and smooth muscles in other situations receive their innervation. The most conspicuous feature of the system is a pair of ganglionated nerve cords, or sympathetic trunks, which extend vertically through the neck, thorax, and abdomen. Each sympathetic trunk is composed of a series of ganglia bound together by short nerve strands. Every spinal nerve is connected with the sympathetic trunk of its own side by one or more gray rami communicantes through which it receives sympathetic fibres for the control of blood-vessels, sweat glands and smooth muscles of the hair follicles situated within the territory of its distribution. The majority of the nerve fibres that take origin in the ganglia of the sympathetic chain are distributed through the gray rami and the spinal nerves.

The thoracic and upper lumbar nerves are connected with the sympathetic chain by white as well as gray rami communicantes. These white rami contain both afferent and efferent fibres. The latter take origin from cells in the gray matter of the spinal cord, travel through the ventral root and white rami, and enter the sympathetic system to terminate in synaptic relation with the nerve cells found in the sympathetic ganglion. They are often designated as pre-ganglionic fibers, whereas those that arise in the ganglia and relay the impulses onward are called post-ganglionic. The gray rami contain post-ganglionic fibres and the white rami contain pre-ganglionic fibres.

The majority of the pre-ganglionic fibres turn either upward or downward in the

sympathetic chain, and run for varying distances within it before ending in its ganglia. The cervical sympathetic trunk is composed exclusively of pre-ganglionic efferent fibres, derived through the white rami from the upper thoracic nerves and ascending to terminate in the cervical sympathetic ganglia. The lumbar and sacral portions of the trunk are composed in the major part of descending fibres derived through the white rami from the lower thoracic and upper two lumbar spinal nerves.

Those fibres of the white rami which are concerned with the innervation of the abdominal viscera pass into the splanchnic nerves and end in the celiac ganglion. These fibres reach the splanchnic nerves after passing through the lower half of the thoracic sympathetic chain but they are not interrupted in the chain ganglia through which they pass. These fibres reach the viscera by following the arterial supply to these organs or by direct extension as post-ganglionic fibres from their various plexiform arrangements or sympathetic ganglion. The thoracic viscera receive their post-ganglionic sympathetic rami from the upper thoracic sympathetic chain in a similar arrangement.

The autonomic nervous system, in addition to the sympathetic thoracicolumbar outflow, contains two streams of pre-ganglionic visceral efferent fibres called the parasympathetic system: the cranial stream arises from the third, seventh, ninth and tenth cranial nerves, the sacral stream from the second, third and fourth sacral nerves.

According to Ranson[29] and Kuntz[25] most of the sympathetic nerves contain, in addition to the fibres already considered, sensory fibres, which convey impulses from the viscera to the spinal cord. These sensory fibres have their cells of origin in the spinal ganglion and reach the sympathetic system by way of the white rami. Visceral reflexes therefore travel arcs of at least three neurons each. The impulses reach the spinal cord along visceral afferent fibres through white rami and the dorsal roots. These afferent sympathetic fibres end in sympathetic ganglia, and the impulses which they carry are relayed to involuntary muscle and glandular tissue by post-ganglionic fibres. The ganglia of the sympathetic trunk do not serve as reflex centres, but only as relay stations[27] in the conduction pathways from the spinal cord to the viscera.

The vasomotor innervation of the arteries of the extremities was once believed to be centrifugal[26] in its arrangement, but the work of Kramer and Todd,[22] and Potts[28] has proved rather conclusively that the distribution corresponds to the musculocutaneous somatic distribution, except for short distances where the principal arteries leave the aorta. Therefore, it is apparent that complete vasodilating effects are accomplished only when all vasomotor fibres are interrupted by section of a sympathetic trunk, by ganglionectomy or by complete ramisection.

Historical Data.—Surgical procedures performed on the sympathetic nervous system date back to 1899, when Jaboulay[20] attempted to relieve painful conditions of the lower extremities by performing periarterial sympathectomy. This procedure was not given serious consideration until Leriche[24] reported his experiences in 1913, when he advocated periarterial sympathectomy for numerous peripheral vascular, trophic and painful lesions.

Royle,[30] in 1924, advocated and performed ramisection for relief of spasticity of the muscles of the extremities, but difficulty was encountered in duplicating his results. Adson has obtained some reduction of the spasticity by abdominal transperitoneal lumbar sympathetic ganglionectomy and trunk resection, which he first performed May 20, 1924. However, he is inclined to believe the results are due to the increased blood supply following thorough interruption of vasomotor fibres, rather than to section of sympathetic nerves to striated muscle, for numerous investigators doubt the existence of sympathetic innervation of striated muscle in mammals. Orbeli[27] believes that the sympathetic fibres augment cerebrospinal responses. Von Gaza,[19] in 1924, Archibald,[2] in 1928, and Scrimger,[31] in 1929, performed paravertebral ramisection of the splanchnic nerve for visceral pain, with some success. This problem is undergoing much investigation at this time.

Adson,[3] and Davis and Kanavel[16] were among those who attempted to duplicate

the results of Royle reported in 1924. May 20, 1924, Adson employed the method mentioned in the preceding paragraph, and it was following this that he observed that the temperature of the skin of the lower extremities remained permanently increased. Royle reported that cutaneous temperatures in the first case in which he performed ramisection remained only temporarily increased, but later stated that a slight increase remained permanently. This suggested that the more extensive operation of ganglionectomy and trunk resection included all of the vasomotor fibres to the extremities. This phenomenon reopened the field of surgical treatment of peripheral vascular diseases. Davis and Kanavel, and Diez[17] and Fulton[18] subsequently reported experiences similar to Adson and Brown's following ganglionectomy and trunk resection.

In 1924, pre-operative and post-operative calorimetric studies were made by Brown[11, 12] of patients on whose sympathetic apparatus Adson operated for spastic conditions. The report showed that elimination of heat following operation had increased on an average of 400 per cent., and that this increase had remained permanent. These data suggested the practicability of applying surgical procedures in vasospastic diseases, and such an operation was carried out with success by Adson,[4] March 19, 1925, in a case of Raynaud's disease of the lower extremities. Subsequent study of this patient and of others has shown that vasodilatation has remained, and that the patients have been free from all symptoms. Adson first carried out cervicothoracic ganglionectomy and trunk resection by the posterior[5] approach July 31, 1928. Following success in the treatment of Raynaud's disease patients with other diseases in which vasospastic phenomena were manifested were likewise subjected to the operation. Before these operations could be performed, however, it was apparent that some measure had to be devised to determine, before operation, the degree of vasomotor spasm present, and whether this spasm could be sufficiently relaxed to justify the surgical procedure.

The studies of capillaries made by Brown[10] offered some assistance, but the variations in temperature indicating flow of blood served as a better index. Therefore, Brown[11] introduced studies of cutaneous temperatures.

Vascular Studies.—We can record only relative estimates of volume flow of blood; the number of capillary loops to a given field, the rate of flow of the corpuscles, and the elimination of heat and the temperature of the skin that are dependent on the flow of blood can be determined. By the Stewart-Kegerreis calorimeter it was possible to estimate the radiation of heat before and after operation, but it was not until Brown,[13, 14] suggested recording the temperature of the skin before fever had been induced, and during its course, that there was any accurate knowledge concerning vasospasm. The thermocouples of the electrothermometer are fastened to the various portions of the fingers, toes, hands, feet and body, in preparation for readings of surface temperature. First, readings are recorded of the temperature of the room, and of the mouth and surface of the skin. Thus, corrections can be made for the environmental temperature, and the temperature of the mouth and skin can be compared with the corresponding temperatures of a normal person, and with the readings taken during the height of fever. The fever is produced by administering, intravenously, a foreign protein, for example, 5,000,000 to 75,000,000 triple typhoid vaccine. The dose depends on the weight and sex of the patient. Hourly readings are made until the maximal rise of fever has been obtained. These readings are compared with the initial temperatures, to determine the ratios of increased temperature. General, regional, and spinal anæsthesia produce vasodilator effects and can be employed instead of administration of protein.

In studying the temperature of a normal person, it will be observed that the temperature of the mouth may have increased as much as an average of 2° C., whereas the temperature of the skin over the digits will have increased 4° to 6° C., or two to three times the mouth temperature, indicating that the peripheral arteries have been opened by inhibition of the vasomotor centre and that more blood has been permitted to flow to the periphery. In cases of vasospastic disorder, the difference in temperatures is still greater, since the initial surface temperature of the digits is lower than that of a normal

subject exposed to the same room temperature. In cases of general arterial sclerosis there may be little, if any, difference in the skin temperatures before and after administration of the foreign protein, indicating that the vessels are incapable of relaxing to allow increase of the flow of blood to the periphery. In cases of thrombo-angiitis obliterans it is possible to determine whether there exists an element of vasomotor spasm of the collateral vessels and unoccluded arteries; it is possible, too, to determine, by individual readings, the condition of each digit. Therefore, the test serves as an index, and unless the rise in temperature of the skin of the digits is two or more times greater than the rise of the oral temperature, the condition is considered inoperable. The test also permits determination of the degree of collateral circulation in different portions of the same digit. This aids us in arriving at a prognosis concerning the preservation or loss of digits with ulceration.

Further to substantiate the opinion that vasomotor spasm exists and is due to stimuli of central origin carried over post-ganglionic gray rami to the arteries instead of being due to a local fault[32] in the arterial walls, we have observed that increased blood flow with resulting increased temperature is readily produced by anæsthesia of the vasomotor nerve by nerve block, and regional and spinal anæsthesia. In cases of Raynaud's disease the color changes are immediately abolished by anæsthesia, and during the anæsthesia they cannot be reproduced by emotional stimuli or exposure to cold. Similar results are obtained by a thorough interruption of gray rami which is most effectively accomplished by removing the sympathetic ganglia with resection of trunks carrying vasomotor fibres. Following cervicothoracic ganglionectomy the retinal arteries and veins have been found to be dilated from one and a third to one and a half the pre-operative size. Repeated calorimetric and cutaneous temperatures in cases of sympathectomy have revealed that the increased blood flow has been maintained for seven years in the cases in which operation was first performed. The real problem is to select suitable cases for operation and to decide when operation is indicated. It is obvious that vasodilatation cannot be produced in an arteriosclerotic or occluded artery, and that surgical intervention is useless unless there is positive evidence of vasospasm in the remaining nonoccluded arteries. The operation is not indicated in the milder cases, in those that respond quickly and favorably to medical treatment, nor in cases of massive gangrenous lesions, but is indicated for the slowly progressive lesions.

Surgical Technic.—Inasmuch as the surgical technic has been described previously,[3, 4, 6] we shall not go into details as it is generally accepted that the vasomotor innervation of the arteries and veins does not run centrifugally along the vessels, but that the vessels receive their innervation at various levels corresponding to the musculocutaneous segments. Although Leriche[24] conceived the idea that vasodilatation might be accomplished by interrupting the vasomotor fibres by a peri-arterial stripping operation, the operation was not of sufficient scope to include all of the nerves. If the vasomotor fibres are divided by ramisection or ganglionectomy and trunk resection,[5, 6] it is immaterial which method is used so long as they are completely resected. In treating peripheral vascular diseases of the toes and feet we prefer to use the abdominal transperitoneal approach which permits removal of the second, third and fourth lumbar sympathetic ganglia with the intervening trunk through an abdominal incision. In sympathectomy of the vessels of the fingers and hands we choose the posterior approach,

resecting a portion of the first rib and the transverse process of the first thoracic vertebra on each side in order to enter the mediastinum and remove the inferior sympathetic cervical and first thoracic ganglia with the upper portion of the thoracic trunk. Occasionally, we can include the second thoracic ganglion through the same incision. When we are unable to include this ganglion we divide all ascending rami to the first thoracic and eighth cervical nerves. We believe this operation to be more thorough than the anterosuperior approach since it is difficult to include all of the vasomotor fibres in the gray rami coming from the second and first thoracic ganglia by the anterior and superior approach.

Raynaud's Disease.—Mild[1] vasospastic phenomena such as cold, moist hands and feet, or symmetric pallor of one or more digits without pain, numbness or trophic changes can scarcely be interpreted as constituting the symptoms of Raynaud's disease, although in such cases the physiopathological state is identical to that in Raynaud's disease. The diagnosis of Raynaud's disease is reserved for cases in which there is symmetric pallor, followed by cyanosis in which it is difficult to induce recovery, and in which the patients complain of numbness and aching pains during the stages of pallor. This condition is most common among young, asthenic women and among women of middle life who are chronically fatigued and subjected to severe mental strain. The milder forms of the disease rarely require special treatment and these milder forms may be controlled by improving social and economic states, such as avoiding certain social contacts, making new friends, avoiding overfatigue, changing occupation, changing climate, or wearing warmer clothing. The severe types continue to progress in spite of medical measures, and trophic changes appear, such as deformed nails, dry ulcers, scleroderma, and occasionally gangrene of the digits.

When medical treatment is inadequate, surgical procedures are instituted with the purpose of relieving vasomotor spasm. Following the interruption of all vasomotor fibres, the pain disappears, swelling subsides, ulcers heal, nails grow, the characteristic color changes disappear, arterial pulsations increase, and the skin appears normal, pale pink and distinctly warmer and drier. However, cyanosis has been seen to occur in fingers with ulcerated tips when held in dependent positions and exposed to cold following sympathectomy. Ulcers heal and do not recur.

In[3] order to evaluate the results of sympathectomy in the treatment of Raynaud's disease in its various degrees of severity, cases have been classified in three groups. In the first group the cases are uncomplicated and the patients complain of asphyxia and cyanosis associated with paræsthesia. In the second group are more advanced cases of active ulceration. In the third group are the most advanced cases in which ulcer or gangrene is associated with marked evidence of scleroderma and arthritis.

A review of Tables I and II will show that the disease affects the upper extremities more often than the lower, and that the results from lumbar sympathectomy are better than those from cervicothoracic sympathectomy. The incomplete results in the fingers are apparently due to failures to include all of the vasomotor fibres when using the second rib approach, or to the

advanced stage of the disease which has produced permanent changes in the peripheral circulation which does not permit vasodilatation of the arterioles or return to normal of the tremendously dilated capillaries.

TABLE I

The Incidence of Raynaud's Disease in the Sexes, Average Age, Duration of Disease Previous to Sympathectomy, the Relation of the Involvement to the Upper and Lower Extremities, and the Number of Operations Performed

Group	Type of Disease	Cases	Age, Years	Male	Female	Average Duration of Symptoms, Months	Average Duration Since Sympathectomy, Months	Cervicothoracic Sympathectomy	Lumbar Sympathectomy
1	Uncomplicated	16	33.6	1	15	58.6	34	11	5
2	With ulcers	6	25.7	0	6	71	40.7	3	3
3	With ulcers or gangrene with scleroderma and arthritis	32	33.0	3	29	79	25.7	25	7
	Totals	54	30.7	4	50	69.5	33.2	39	15

The post-operative sequelæ of these surgical procedures result in dryness of the skin, which can be relieved by application of lanolin and cocoa butter. Horner's syndrome of apparent enophthalmus, contracted pupils, and lagging of the lids due to relaxation of the musculus tarsalis is not a serious disfigurement if it is bilateral, nor does it interfere seriously with vision at night. Resection of the upper portion of the thoracic sympathetic trunk, and of the corresponding ganglia, does not alter materially acceleration of the heart, and none of the patients subjected to the procedure has complained of cardiac symptoms after operation. There have been no deaths to date.

Thrombo-angiitis Obliterans.—Thrombo-angiitis[7] obliterans is a peripheral vascular disease, characterized by thrombosis of the peripheral arteries and veins, resulting in intermittent claudication, localized pain, œdema, ulceration and gangrene of digits, and in the later stages of the disease,[6] massive gangrene. Besides the process of thrombosis vasomotor spasm of the principal unoccluded and collateral arteries is found, which aggravates the symptoms produced by the occlusion of arteries and veins, and which, if relieved, ameliorates the symptoms, preserves digits and extremities, and aids materially in rehabilitating the patient.

The specific etiology is still undetermined. Some investigators hold that the disease is due to specific infection or to toxic agents. It is most common among young men who are engaged in active exercise, but it also occurs

TABLE II

Results from Cervicothoracic Sympathectomy or Lumbar Ganglionectomy and Trunk Resection for Raynaud's Disease

Group	Type of Disease	Case	Average Relief of Color Changes; Per Cent.	Average Relief of Pain; Per Cent.	Average Healing of Ulcers; Per Cent.	With Recurrent Signs	With Incomplete Sympathectomy
	Cervicothoracic Sympathectomy (39 cases)						
1	Uncomplicated	11	85	85	No ulcers	None	None
2	With ulcers	3	60	60	100	1	1
3	With ulcers or gangrene with scleroderma and arthritis	25	85	75	85	4	4
	Lumbar Sympathectomy (15 cases)						
1	Uncomplicated	5	100	100	100	None	None
2	With ulcers	3	100	100	100	None	None
3	With ulcers or gangrene with scleroderma and arthritis	7	90	90	90	None	None

among men occupying sedentary positions, and occasionally it has occurred among young women. It is supposed to be more prevalent in the Hebrew race, but it has been found to develop in all races. Some investigators believe that the use of tobacco, especially if in excess, is a causative factor. The exposure to cold has a deleterious effect on the patients.

Symptoms.—Intermittent claudication is one of the earliest symptoms and undoubtedly is due to anoxæmia brought on by exercise or excessive fatigue. This is followed by or associated with postural color changes, that is, rubor with dependency and pallor with elevation. As the disease progresses, localized pain such as pains in the arches of the feet may be present during the period of rest. Trophic changes are manifested by nonhealing abrasions from trauma, ulcerations of digits, and the development of localized or massive gangrene. The disease usually progresses slowly and may remain temporarily quiescent in any one of the earlier stages. In some cases the disease never progresses to ulceration and gangrene, whereas in others the symptoms respond favorably to medical treatment, but more often it slowly involves the opposite extremity. In reviewing this series of 240 cases of thromboangiitis obliterans, it was found that the disease involved the lower extremities in 60 per cent.; it affected the upper extremities alone in 2 per cent., and both upper and lower extremities in 38 per cent. It further was observed

that the disease would sooner or later become bilateral even though more prominent in one extremity. In reviewing these statistics of cases it was learned that the disease was bilateral in 98 per cent. of the cases.

Marked improvement followed active medical treatment in 56 per cent. of the cases, and the incidence of amputation of leg or hand which was 25 per cent., in cases in which treatment was inadequate or not given, had been reduced to 14 per cent. Although medical treatment has been effective and the incidence of amputation has been lowered, the disease progressed in many of the cases, and we were stimulated to look for more effective methods of treatment. This, then, led to the employment of sympathetic ganglionectomy and trunk resection for a group of patients suffering with this disease. Since we had no criterion to follow in the selection of suitable cases at the beginning of the investigation, we were compelled to progress by trial and error. As experience developed we found we can determine pre-operatively the patients who will respond to sympathectomy, since we can reproduce the increased blood flow with the increased skin temperatures produced by vaccine therapy and have found that these effects remain continuously increased, whereas the effects of vaccine therapy are only temporary.

Selection of Cases.—On admission and during examination these patients are classified according to an outline proposed by Brown, Allen and Mahorner.[13]

Slow Progression.—This is the most common type. Coldness of the feet is usually the first symptom, followed by excessive fatigue of single digits, the arch of the foot, the wrist, ankle, calf, or forearm. Excessive fatigue gradually changes into and is replaced by the pain of claudication occurring in similar areas which progresses and produces an increasing degree of disability. Color changes with change of posture are followed by trophic changes which occur spontaneously or are incited by incision of toes, removal of toenails, accidental trauma, amputation of toes, or the application of blistering ointments. With the occurrence of trophic changes the pain is sharply accentuated and becomes almost unbearable. The gangrenous areas increase in extent requiring amputation, or healing may occur in a group in which pain can be relieved. The extremities are cold, there is excessive pallor with elevation and abnormal rubor with dependency. Pulsation in the arteries is diminished or absent. The entire process is completed in from four to eight years.

Absence of Progression.—In this type mild symptoms of vascular insufficiency (excessive fatigue or the pain of claudication) progress slowly for a time and then remain stationary. The extremities are cold, the arteries are obliterated, and postural color changes are present. Trophic changes other than proliferation of the nails and increased thickening of the skin over the weight-bearing area do not occur. Disability is minimal in spite of symptoms which may have endured from eight to twelve years.

Circulatory Compensation.—This type is not widely recognized although it is fairly common. Shallow ulcers do not progress and after from six months to a year healing occurs. Gradually other symptoms largely dis-

appear, leaving the patient with extremities approximately 80 per cent. adequate for all needs. With care patients in this group may go on indefinitely with extremities functioning sufficiently well for all ordinary needs. Weber[33] has noted the return of pulsation in an obliterated radial artery and this has been observed in several of our cases.

Acute Fulmination.—In this type the clinical syndrome is the antithesis of slow progression. Claudication appears relatively suddenly and progresses rapidly. The rest pain is severe before gangrenous changes occur and greatly accentuated afterward. Œdema and lymphangiitis are present around the gangrenous area and there may be slight fever and leucocytosis. The gangrene progresses rapidly, the pain is unbearable and intractable to all measures. Amputation is necessary. The process may be complete after from three months to one year.

On completion of the examination which includes laboratory and vascular studies, we decide on the course of treatment, basing our judgment not only on the condition of the vascular system but on the present status and course of the disease. As previously stated, the operation is not employed in mild cases without ulcers; neither is it employed in cases in which there has been no progression nor in which the circulation has become compensated. It is never wise to urge operation during the acute stage of inflammation with active cellulitis. This type of patient should be hospitalized and treated medically from three to six weeks.

The slowly progressive cases which include most cases of thrombo-angiitis obliterans are most suitable for sympathectomy, and even then when extensive ulcers or gangrenous digits are present, we are inclined to hospitalize patients for two or three weeks under vaccine therapy in order to determine how the individual patient is going to respond to the vasodilating effect obtained by administration of protein before sympathectomy is performed. If the disease affects both the lower and upper extremities we usually carry out sympathetic ganglionectomy and trunk resection to interrupt the vasomotor fibres to the extremities affected first and then wait six weeks until the patient has thoroughly recovered before performing the second operation. We usually perform bilateral sympathectomy even though the disease appears to produce symptoms in only one extremity, since ultimately it is almost sure to involve the opposite extremity, and since sympathectomy has apparently controlled the process and preserved the opposite extremity. However, recurring phlebitis may develop in either extremity following sympathectomy, but this, aside from producing localized pain and œdema, does not jeopardize the life of the extremity.

Results.—A review of the statistics of 100 consecutive cases of thrombo-angiitis obliterans in which sympathetic ganglionectomy and trunk resection had been done disclosed that bilateral lumbar operation was done eighty-nine times and cervicothoracic ganglionectomy fifteen times. Four patients were operated on for thrombo-angiitis obliterans for both the upper and lower extremities, which accounts for the 104 operations. The series included

ninety-six men and four women; their average age on admission was thirty-five years. The average duration of symptoms on admission was four years. The legs had been amputated in sixteen cases, an arm had been amputated in one case and in several cases toes had been amputated previous to admission. Sixty-three patients complained of intermittent claudication, sixty-one of whom had obtained 85 per cent. relief of symptoms. Eighty-three patients complained of rest pain, of whom sixty-nine obtained 85 per cent. relief. Twenty-five complained of continued pain or the development of recurrent pain following sympathectomy. Twelve patients had œdema of the extremity involved, seventy-seven came for observation complaining of ulcers, thirty-four had gangrenous digits, and three had massive gangrene of the extremity. In ten cases following sympathectomy recurring phlebitis developed, in nine ascending arterial occlusion developed which was probably due to the fact that the patient was operated on during an acute stage of ascending thrombosis. Recurring ulcers or gangrene developed following operation and dismissal in seven cases; in this group five legs and one foot were amputated. Eighty-seven patients were markedly improved following sympathectomy, receiving an average relief of 80 per cent., and seventy-six patients obtained a useful extremity. In the absence of trophic lesions sympathectomy checked the progress of the disease in the opposite extremity in every case. Seven patients still complained of symptoms of neuritis, two of whom were subjected to chordotomy with only moderate success; one patient had a leg amputated and others had cutaneous nerves divided without success. Five patients had post-operative pneumonia, and two of them died. One patient died from a pulmonary embolism. Two patients died from cardiac failure immediately following operation, and the sixth patient never recovered from the results of the anæsthetic (ethyl [1 methylbutyl] barbituric acid).

The only deaths that occurred from sympathectomy in the treatment of Raynaud's disease, thrombo-angiitis obliterans and scleroderma occurred in cases of thrombo-angiitis obliterans. It would appear that the lesion is not only confined to the peripheral arteries of the extremity but probably also affects terminal arteries in other organs, as it was demonstrated in the two deaths from cardiac disease.

Scleroderma.—Adson, O'Leary and Brown,[8] in 1929, stated that a third of the patients who consult a dermatologist for scleroderma give a history of vasospastic phenomena simulating Raynaud's disease. Scleroderma also may accompany thrombo-angiitis obliterans and certain types of arthritis. The vascular spasm in scleroderma is more or less continuous, and produces a constant reduction of the supply of blood to the extremities.[14] Since the spasm and cyanosis can be temporarily relieved by application of heat, by the use of general, spinal, and regional anæsthesia, and by the administration of vaccine, this condition was studied in a manner similar to that in which Raynaud's disease was studied. The changes in scleroderma simulate these that arise from a plaster cast that is too tight; namely, cyanosis, swelling,

pain, atrophy, contracture, deformities, and disuse. This type of scleroderma differs from the amorphous type in that the disease affects chiefly the skin over the hands, forearms, face, neck and scalp. The atrophy and contracting processes of the skin are associated with similar processes in the underlying structures, and it is not unusual for a patient to complain of weakness, inability to use muscles, and inability to open the mouth or protrude the tongue. Arthritic changes often become manifest in the fingers; this condition is referred to as sclerodactylia. The changes associated with scleroderma are more pronounced in the skin of the uncovered parts, such as the hands, forearms, face and neck, than they are in the covered parts, which suggests that reflex stimuli of cold accentuate existing vasomotor spasm. The fact that underlying tissues are subjected to atrophic changes suggests that vasospasm is not confined to the vessels of the skin, but that it does interfere with the circulation of all tissues.

Care should be exercised in selecting suitable cases, since the hide-binding process of scleroderma strangulates and destroys capillaries and arterioles which naturally cannot be opened by a vasodilating procedure. The vasomotor index again serves its purpose in the selection of operable cases. The post-operative results are dependent on the stage of the disease. The vascular phenomenon is corrected, as in Raynaud's disease, and rehabilitation of skin and adjacent tissues will take place if vasomotor spasm is present, and not too many capillaries and arterioles have been destroyed. If it is not possible to demonstrate the desired increase in surface temperature by administration of protein, little is to be expected from operation. Ankylosed joints are not made flexible by sympathetic ganglionectomy and trunk resection. It is wiser to choose the earlier cases for operation; improvement is more likely to occur in these cases than in advanced cases in which deformity has taken place.

Results.—The cases were divided into three groups and classified on the basis of the relationship of the vasospastic phenomena to the development of the disease. In the first group were cases of primary scleroderma with vasomotor phenomena developing late in the disease; in the second group were cases in which scleroderma and vasomotor disturbance developed simultaneously. In the third group vasomotor disturbances preceded the development of scleroderma.

In the first group the vasomotor phenomena were improved, the skin temperature was increased, the skin became more flexible and ulcers healed, but the result could not be compared with that in the third group; the outstanding accomplishment was the checking of the disease with an average improvement of 10 per cent.

In the second group the results were similar to those in the first group, added to considerable restoration of function, with an average improvement of 25 per cent.

In the third group recoveries following lumbar sympathectomy averaged 85 per cent. whereas following cervicothoracic sympathectomy they averaged 45 per cent. In this group the skin not only became pink, warm, soft and

flexible but the muscles again became fusiform and flexible which resulted in improvement of strength. Patients who had been unable to open their mouths or protrude their tongues were again able to masticate their food as formerly. The skin still remained very thick and bruised easily; ankylosed joints were unchanged.

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DISCUSSION.—DR. ARTHUR W. ALLEN (Boston) remarked that the general management of peripheral vascular lesions cannot be overemphasized. Unless one is willing to go to the trouble of caring for these individuals in a standardized, routine way, then operations and various other forms of specific therapy are likely to fail. It also has another bearing on the subject. If one places these people under observation, under ideal circumstances, with certain routine procedures, looking after their general hygiene, fluids, food, exercise, and so forth, one will find in a very large percentage of the arteriosclerotic, particularly those associated with diabetes, and in a certain number of cases of thrombo-angiitis obliterans, that they will lose their so-called rest pain in a period of a week or ten days and from then on one's treatment may be varied accordingly, and general measures may be all that are needed.

They had had a good many failures in their cervicodorsal sympathectomies. The cases presented here had all been operated upon more than one year ago.

They have had under observation in a three-year period over 400 cases of peripheral vascular lesions. Thirty-seven of these have been what are called primary vasomotor disease or Raynaud's disease. Fifty-one they have classified as secondary vasomotor inbalance with scleroderma in some cases; certain types of arthritis, and so forth. Eleven of these primary cases of vasomotor inbalance or Raynaud's disease have been subjected to sympathectomy. All of these patients have been incapacitated at the time of the operation. Fifteen cervicodorsal operations and eight lumbar operations have been done on these eleven patients. In the cervicodorsal operations there have been eleven returns of vasomotor control. In the secondary group the results have been somewhat better. There have been ten of these patients. Nine have had cervicodorsal sympathectomy and five lumbar sympathectomy. There have been three cases that have reëstablished vasomotor control in the cervicodorsal region.

A summary of the twenty-one patients in both the primary and secondary groups: there were twenty-four cervicodorsal operations; with a return of vasomotor influence in fourteen sides, in eight patients.

These results are somewhat discouraging. None of the lumbar ganglionectomies has shown any signs of return of vasomotor control. All of these had vasomotor influence eliminated, as shown by sweating tests immediately after the operation. All had a very high vasomotor gradient.

In eighty-eight patients with thrombo-angiitis obliterans under observation, not very many have been found in whom it was felt that operations upon the sympathetic nervous system would be of benefit. Perhaps they have overlooked opportunities along this line, but most of these individuals who do not have rest pain or open lesions will respond to general routine measures and certain palliative ambulatory procedures which have been described elsewhere.

The group that is incapacitated with rest pain, with open lesions and painful ulcerations has not in their hands been relieved of their pain by ganglionectomy. They have, therefore, resorted in twenty-nine cases in this group to peripheral nerve block as described by Smithwick and White. In this very advanced, hopeless group of thrombo-angiitis obliterans, the results have been very much better with the nerve block than with any other procedure which they had found, although in the twenty-nine cases so treated there had been eleven major amputations.

Dr. Martin B. Tinker (Ithaca, N. Y.) emphasized the great relief some chronic arthritis patients experience. A patient under his care, who had used sedatives every night for over six months, was immediately relieved and even post-operatively did not require sedatives.

Another point which had impressed him was the ease of the approach by the incision suggested by Doctor Robertson. He had been convinced that the retroperitoneal approach was simpler and safer than the transperitoneal. In two operations within a week after seeing Doctor Robertson's work he had found these patients so surprisingly free from post-operative discomfort, the approach so easy, and it was so easy to expose the sympathetic chain, that he believed personally it is the method of choice.

Dr. Howard Lilienthal (New York City) expressed a hope that the gentlemen who contributed to this discussion would tell him why the people who have thrombo-angiitis obliterans are in so enormous proportion, practically all males. He knew that those we see for the most part come from Central European countries and from Southern Russia.

He also knows that the women in this region are not addicted to smoking, as are the men.

Many years ago, when Dr. B. Sachs and Dr. Alfred Wiener first called attention to the fact that this disease, thrombo-angiitis obliterans (which had another name at that time), was a disease of vascular and not merely arterial origin, the question of tobacco as a cause was first considered.

Dr. Harry H. Kerr (Washington, D. C.) was convinced that the question of success following sympathectomy or ganglionectomy was a question of surgery. He said the more thoroughly the ganglia are eradicated, with all their branches, the better the results will be. His largest experience had been in operations for angina pectoris. As his experience develops he is doing more thorough eradications, and getting better results. This is made possible by injection of the ganglia with normal salt solution through a very fine needle. The injection brings out all the branches so that eradication is much more perfect. There was another type of case apparently susceptible to sympathectomy which he would like to put on record. It is sympathectomy for retinitis pigmentosa. Retinitis pigmentosa is a familiar disease characterized by gradual, on-coming blindness, progressive narrowing of the visual fields, and the deposition of pigment in the periphery of the retina. Thoracicocervical sympathectic resection had been reported.

He operated on a case of retinitis pigmentosa by superior cervical sympathectomy. This operation seemed a more direct attack on the sympathectic supply of the eye. The result was dramatic. The patient had visual fields of under 10 degrees; after operation they were increased to between 30 and 40 degrees. His visual acuity, which before operation had been 20/100, went up to 20/40. He operated on another case with apparently not so good results. Possibly incomplete surgery was responsible.

Dr. William Jason Mixter (Boston) noted a marked lack of uniformity in the testing of patients with vascular disease and one finds a considerable difference of opinion in the interpretation of results. As time passes and the methods of testing become more uniform the interpretation of these tests will be more uniform also.

The results of operations on the cervicodorsal ganglion have not been altogether satisfactory as there have been a good many recurrences. This is due he believed in part to the difficulty of complete exposure of this ganglion. Complete removal of this ganglion together with the ganglia lower down in the chain is essential. Doctor Harvey and Doctor Oughterson indicate in their work that partial extirpation is not sufficient.

For cervicodorsal ganglionectomy he had been using a transverse incision running from shoulder to shoulder in the form of an arch. This incision is more satisfactory than the longitudinal incision.

There has been no tendency to the recurrence of vasomotor spasm following lumbar ganglionectomy which places this procedure on a much more satisfactory basis.

In Boston there have been done comparatively few lumbar ganglionectomies for thrombo-angiitis obliterans. They have seen good results from peripheral neurectomy or alcohol block. The results of these minor peripheral operations have been very good and they certainly have a place in the treatment of thrombo-angiitis obliterans.

Dr. Rudolph Matas remarked that Dr. Mont Reid had referred to oscillometry as an index to the efficiency of the peripheral circulation. The speaker had found an invaluable method of determining the differential blood-pressure in the extremities; and the reason, perhaps, why it has not become more popular and generally utilized in this country, even by those who recognize its value, is that many believe it necessary to use the highly sensitive, but more expensive Pachon instrument. In his experience any ordinary aneroid used for determining the blood-pressure would do perfectly for this purpose provided it did not leak and that the air in the cuff would be kept under perfect control by a well-adjusted screw valve.

After inflating the cuff, the needle would indicate in millimetres the beginning of the oscillations (systolic pressure) and the end of the oscillation (diastolic pressure) and a record could be made in this way more easily and simply than with an imported Pachon. By the utilization of the ordinary sphygmomanometer of the aneroid type the practice of oscillometry would become more generalized.

Dr. Edwin Beer (New York City) said that they had had large experience in this particular disease, pre-senile gangrene, thrombo-angiitis) in the city of New York. In the years past, major amputations used to be a very common procedure for this condition. Since Dr. Samuel Silbert has introduced the hypertonic saline intravenous method of treatment with nerve block and the use of glonoin in large doses, major amputations are a rarity. He therefore believed that ganglionectomy and peripheral sympathectomy should be used only when more conservative measures have been carefully tried and have failed.

Dr. John J. Morton (Rochester, N. Y.) desired to add to Dr. Coller's contribution on tobacco that they had also noted this vasoconstriction effect but when vasoconstriction is once established in these people, even if one gets them to give up smoking, they will not recover from their attacks, according to their experience.

Dr. Ashley W. Oughterson (New Haven, Conn.) emphasized that it may take some time to get the temperature of the extremity down to its lowest level. In the case reported in his paper while the color changes in the hand were striking, they were not so pronounced as in the feet, and it required exposure to a temperature of 65° for several hours before the lowest temperature could be obtained. There seems to be critical temperatures at which one can demonstrate vasoconstriction when there are only a few remaining fibres. Obviously, it is a quantitative effect, and if there are only a few fibres left, vasoconstriction cannot be demonstrated as easily as when all the fibres are present.

Dr. Mont R. Reid (Cincinnati) said that it seemed to him that we do not take this problem with quite as much seriousness as we should. We are, perhaps, trying to find some method of treatment which will not interfere too much with the normal return of a patient's life. Peripheral vascular disease is a very serious proposition and sacrifices may be just as necessary in the treatment of this condition as, for instance, in the treatment of tuberculosis. In a great many cases of arteriosclerotic disease a very radical change or readjustment of work and mode of life would make it possible for many persons to carry on without ever developing any serious complication. A great many of the spastic and inflammatory conditions, by proper care continued over a long period of time, would become arrested and develop an adequate or more or less adequate collateral circulation.

The sacrifice might have to be as great as it is in cases of tuberculosis, but the analogy is not far-fetched. He said if he had thrombo-angiitis obliterans, he would feel that he had to pay the price of a year or a year and a half of the most extraordinary care to try to stop the process, cause a healing and the establishment of an adequate collateral circulation.

Dr. A. W. Adson said that their evaluation of treatment was based on a study of 640 cases; 400 of these were examined and treated previous to 1924 and 240 have been under observation since 1924 and have been subjected to very careful study. In reviewing this group it was learned that the incidence of amputation of extremities was 25 per cent. in the non-treated or poorly treated group which was lowered to 15 per cent. in the well-treated medical group and 6 per cent. in the sympathectomized group.

During the development of sympathectomy in the treatment of thrombo-angiitis obliterans they were usually offered patients for treatment who could not afford hospitalization or would not respond to medical management but as their experience had grown they had come to select patients who had responded to vascular studies and who had presented distinct evidence of a slowly progressive disease.

He believed that sympathectomy had come to remain as a useful means in the treatment of peripheral vascular disease. He said additional investigation is required before all can agree on the surgical indications.

THE TREATMENT OF TRIGEMINAL NEURALGIA BY THE CEREBELLAR ROUTE

By Walter E. Dandy, M.D.
of Baltimore, Md.

This report is concerned with the treatment of trigeminal neuralgia by the subcerebellar route. Soon after its inception a report of the procedure was read by title at the Richmond meeting of the American Neurological Association in 1925. At that time its advantages had not yet appeared, and the old Hartley-Krause procedure as modified by Spiller and Frazier and others was such a satisfactory and safe procedure it was not then considered to be a substitute for this widely used method of attack. Gradually, however, as the cases multiplied, it was discovered empirically that most of the liabilities which followed the temporal route did not obtain when the nerve was sectioned by the cerebellar route.

In the Archives of Surgery, in 1929, a report of the first eighty-eight cases was presented. At that time the advantages of this method had become apparent. At the present time 250 cases of trigeminal neuralgia have been operated upon by the cerebellar route and it is now used exclusively in our clinic. Since this publication the procedure has been modified in many ways which contribute to both its ease and safety. In the last 150 cases there has been no death either at operation or during their stay in the hospital, and there have been no post-operative complications.

The steps in the operative approach are as follows: A small curved incision is made just back of the mastoid on the side of the neuralgia. (Fig. 1.) A small defect is made in the bone, the mastoid process is rongeured away to, but not into, the mastoid cells. (Fig. 1.) The dura is opened, the cisterna magna is evacuated; the cerebellar lobe is then gently elevated and the fluid evacuated, after which the fifth nerve is in full view and is divided either subtotally or totally as desired. The dura is then closed and the galea and superficial wound reunited. The operation is done either under avertin or local anæsthesia. As a matter of fact, it lends itself very easily to local anæsthesia, with which it can be performed almost painlessly except for the brief moment during which the nerve is sectioned and the pain at that time is really very slight. An advantage of local anæsthesia is that the pain fibres in the sensory root may be identified by their sensitivity when touching them; after these fibres have been divided the remainder of the nerve is insensitive.

Since the report in 1929 the following technical improvements have been made:

First.—Avertin anæsthesia has been substituted for ether, either by inhalation or per rectum. This is a great advantage because there is no swelling

of the cerebellum as obtains with ether and there is therefore ample room for exposure of the cerebello-pontine angle in all cases. Furthermore, it provides perfectly smooth breathing which rarely follows ether, and which is so essential when the sensory root is divided.

Second.—The electrocautery makes it possible to easily coagulate and divide the petrosal vein should this be necessary. (Fig. 2.) This vein is merely pinched with forceps through which the current is passed to obliterate the vessel. The control of the petrosal vein and its branches was really the only element of danger in the operation and this can now be easily and

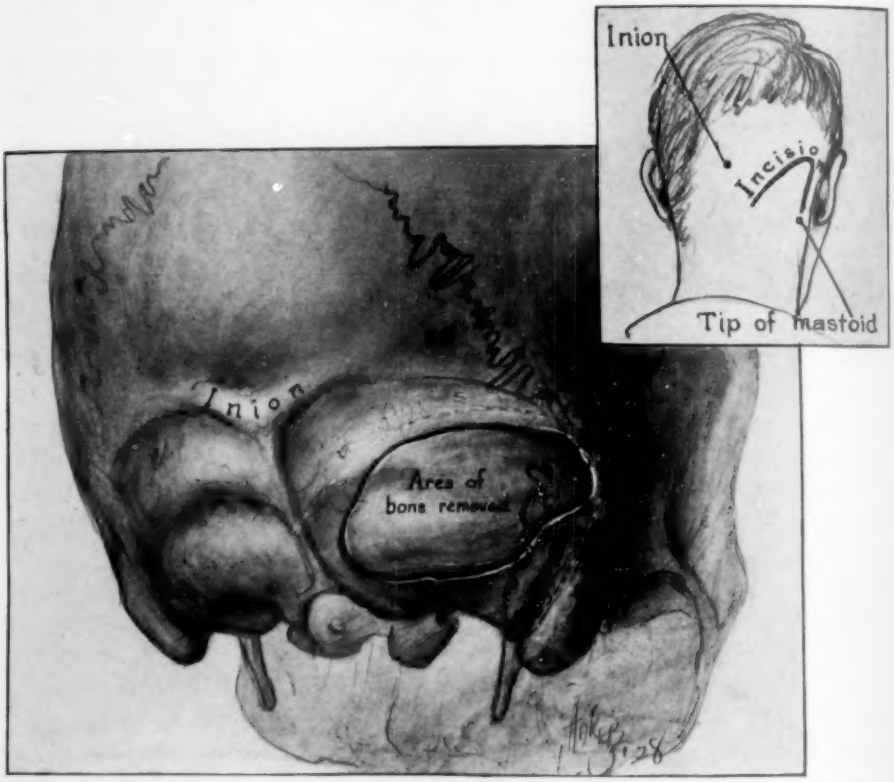

FIG. 1.—Showing cutaneous incision and area of bone removed in order to expose the trigeminal nerve by the cerebellar route.

safely overcome, if necessary, with the cautery. As a matter of fact it is only once in about fifteen cases that it is necessary to occlude the petrosal vein for in the remaining cases the sensory root is not at all obscured by this vessel.

Third.—Suction is now used to evacuate the fluid in the cisterna lateralis; this makes it unnecessary to sponge and, therefore, it not only saves time but avoids any possible injury to the auditory nerve, which lies at a safe distance posteriorly. Suction is applied indirectly through a pledget of cotton that is placed in the cisterna lateralis. (Fig. 3.) It acts, therefore, as through a wick.

Fourth.—Formerly a sharp knife on a long handle was used to divide the sensory root. The division of the sensory root is now performed much more easily and safely by using either a blunt hook or by pinching the nerve with the blades of a long narrow forceps. (Figs. 2 and 3.) It requires very little force to interrupt the nerve fibres.

Fifth.—The dura is always closed over the entire defect. In one of the early cases an intracerebellar hæmorrhage resulted because of trauma to the cerebellum when post-operative vomiting thrust the cerebellum against the sides of the bony defect.

The sensory root may be either partially or totally divided by this pro-

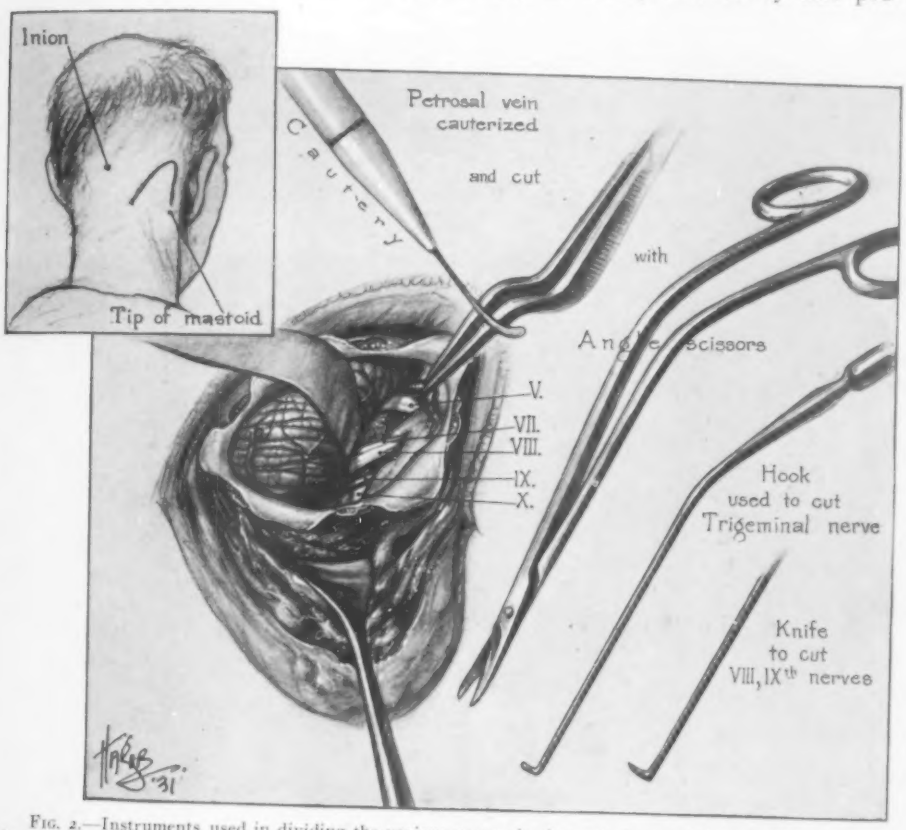

FIG. 2.—Instruments used in dividing the various nerves in the posterior cranial fossa. If necessary the petrosal vein may be obliterated by the cautery. This is only occasionally necessary. The sensory root is usually divided with a blunt hook, or it may be pinched with the forceps.

cedure with equal facility. In my experience the operation is far easier to perform than by the temporal route. The average time required is perhaps one-half hour from the incision to the division of the sensory root, though in many cases it has been performed in ten to fifteen minutes. This is mentioned not as any great point of merit, but because the operative procedure has been frequently criticized as being very difficult and dangerous. In four cases in this series the patients have been over eighty years of age.

The advantages of the subcerebellar route are as follows:

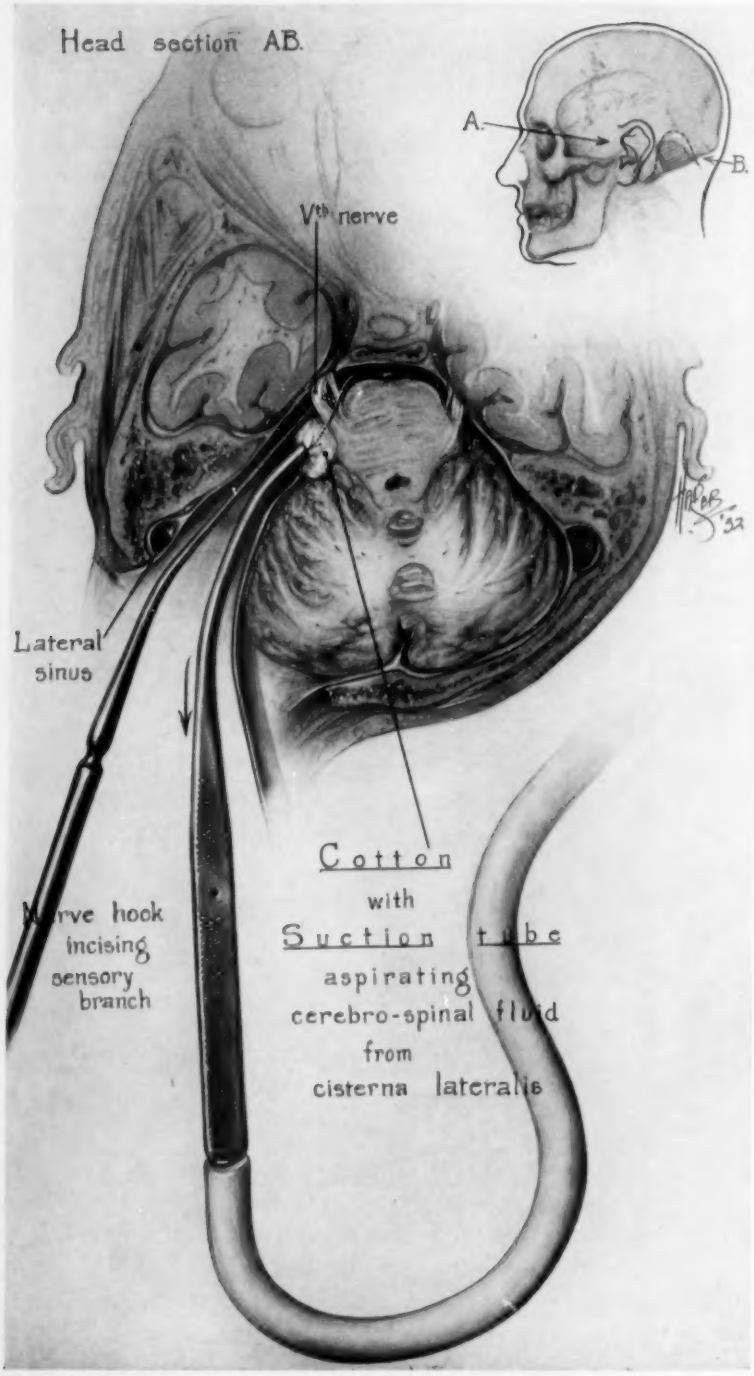

FIG. 3.—Withdrawal of fluid from the cisterna lateralis by suction applied through a pledget of cotton. The diagram shows method of partial division of the sensory root.

(1) In no instance has there been the well-known post-operative keratitis. It has been shown that the incidence of keratitis following soon after section of the sensory root is dependent upon the amount of trauma inflicted upon the nerve. The reason for the absence of keratitis, which is one of the principal complications of the temporal route, is that only a few seconds are required to divide the nerve after it has been exposed. This statement does not mean, of course, that keratitis may not follow at any subsequent time if the eye is injured following a total section of the nerve.

(2) The motor root of the nerve has never been injured since this route has been employed because it is at a greater distance from the sensory root than at any other point in its course. This is of special advantage in operations for double trigeminal neuralgia, of which we have had eight cases. Furthermore, if the patient has double tic douloureux, the pain can be cured on both sides by a single operation using the bilateral cerebellar approach, such as is used in nearly all exposures of cerebellar tumors. Each cerebellar lobe is then elevated in turn and the sensory root divided on each side. By the temporal route two operations are necessary, and, should the motor root be injured on one side a tremendous responsibility would rest upon preservation of the motor branch on the other side.

(3) The facial nerve is never injured because it is at a safe distance. It will be remembered that the facial nerve is injured by the temporal route when the petrosal nerve is torn from the geniculate ganglion in elevating the dura from the floor of the middle fossa.

(4) Another important advantage of the cerebellar route is that in eighteen of our 250 cases tumors have been disclosed in the posterior cranial fossa. (Figs. 4, 5 and 6), and most of these have been removed at the same time the sensory root is divided. In all of these cases the tumor was the cause of the neuralgia and, of course, would have been missed entirely if the temporal route had been used. It is impossible to differentiate by clinical tests those cases in which the tic douloureux is caused by a tumor.

It is worthy of note in passing that in perhaps one-third of the cases of trigeminal neuralgia a gross lesion is disclosed which we think is responsible for the trigeminal neuralgia. Aside from tumors the two common causes are, free arterial loops which lift the sensory root from the brain stem, and the venous branches which cross the nerve, sometimes dividing it into two parts.

The incidence of recurrence in the subtotal section of the sensory root by any method should be mentioned. There have been four recurrences in our series. I have previously shown that division of the posterior half of the sensory root will cure the pain in any branch of the nerve and with practically no loss of sensation. From this observation I have interpreted the findings to mean that the fibres which are responsible for this unique pain are collected from all branches of the trigeminal nerve into the posterior part of the sensory root. However, variations in this distribution must occur and these doubtless account for the occasional recurrences. In one instance there was a recurrence in the second branch when only about one-tenth of the

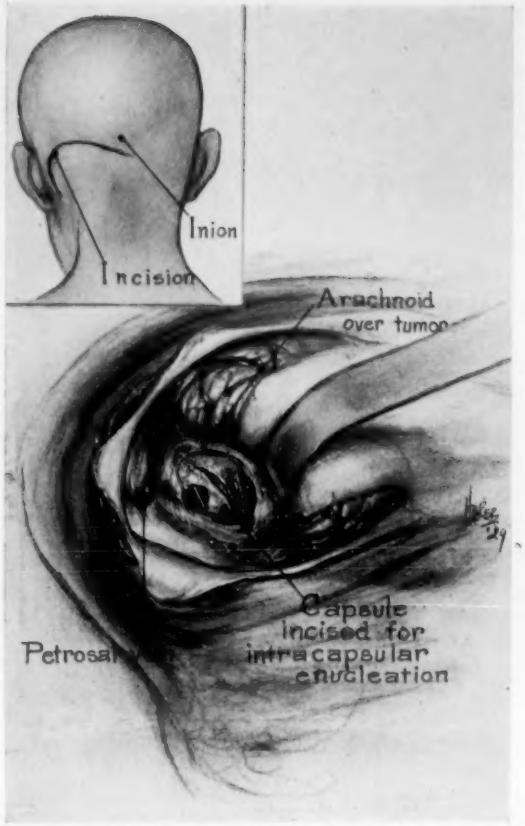

FIG. 4.—Small dural endothelioma in the cerebello-pontine angle causing trigeminal neuralgia.

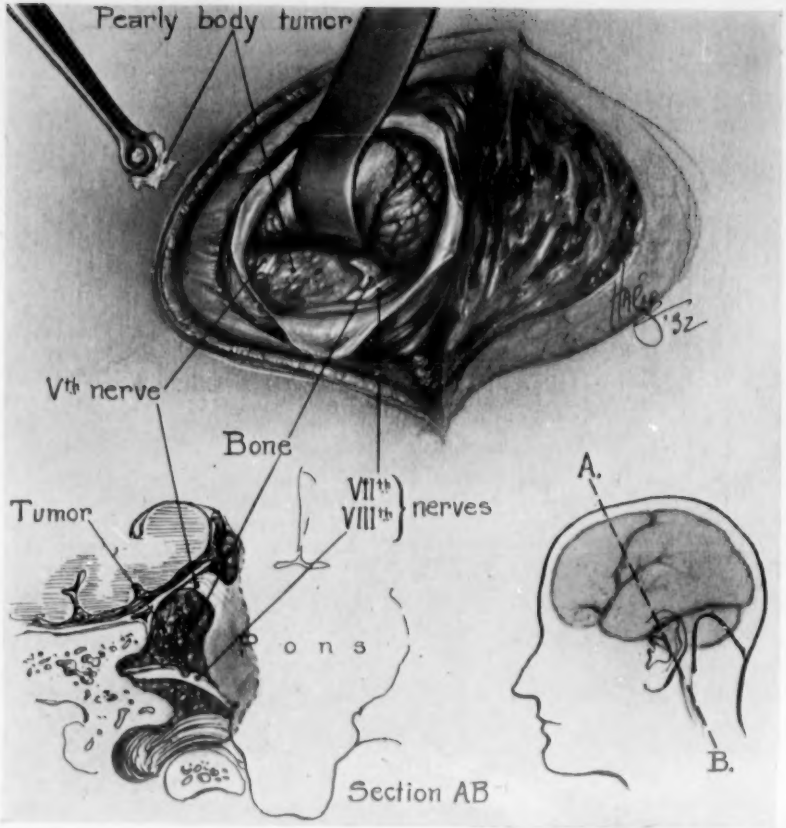

FIG. 5.—Pearly tumor in the cerebello-pontine angle causing trigeminal neuralgia.

anterior part of the sensory root remained. Should a recurrence develop it is a very simple matter to again open the incision, elevate the cerebellum and complete the section of the nerve. The existence of the cisterna lateralis prevents the formation of adhesions and, therefore, there are no difficulties in a second stage at any later time. Because of the possibility of recurrence it is my plan in patients of advanced age to totally divide the nerve rather than to run the slightest risk of another attack. In younger people I feel it is much more important to preserve the sensation of the face intact or nearly so, and run the slight risk which a partial division entails.

Mention should perhaps also be made in this connection of the use of this approach for patients who have carcinoma of the tongue and pharynx. Relief of pain for such patients is not possible by alcoholic injections or by peripheral division of nerves. Such pain is referable to the sensory domain of both the fifth and the ninth nerves, and by the cerebellar approach (under

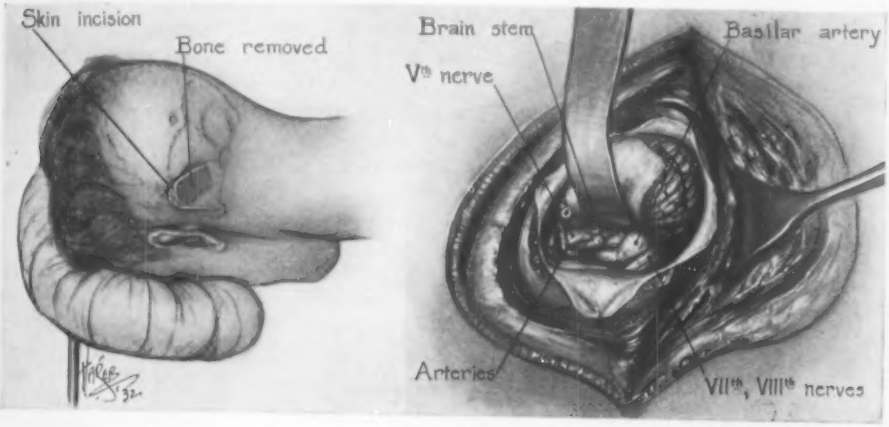

FIG. 6.—Aneurism of basilar artery causing trigeminal neuralgia.

novocaine) both the fifth and the ninth nerves may be divided intracranially and with practically the same ease as obtains for the division of the fifth nerve alone.

The same operative approach is also used in dividing the eighth nerve for Ménière's disease, and the ninth nerve for glossopharyngeal neuralgia.

To Recapitulate.—The operation as now improved, is, in safe hands, one of the safest in cranial surgery. It almost entirely avoids the complications which still follow section of the nerve by the temporal route.

DISCUSSION.—DR. CHARLES H. FRAZIER (Philadelphia) remarked that although the sensory root from the ganglion to the pons in man is but two centimetres long, yet there has been considerable controversy in the past years as to its structure, more specifically as to the arrangement of its fasciculi, first with regard to disassociated forms of sensation such as pain, temperature, and touch, and secondly as to the arrangement of the fasciculi and their relation with the three different portions of the ganglion and the three peripheral divisions.

In Doctor Dandy's paper certain statements have been made with regard to the root at its entrance to the pons. The speaker's experience with the root has been at its entrance to the ganglion, only two centimetres distant. In a recent communication

Van Nouhuys, of Holland (the statement appearing in one of our recent surgical journals), from a study of the anatomical structure of thirty-eight gasserian ganglions which he had dissected anatomically, stated: *First,* that the sensory root of the fifth nerve is not composed of three parts that correspond to the three peripheral branches; and, *secondly,* that the operation of partial section of the sensory root, assuming that the pain is carried by bundles having a definite location, is not based on anatomical facts, and therefore cannot be regarded as an absolutely reliable procedure.

Doctor Frazier was not qualified to pass judgment upon the technic employed in the examination by Van Nouhuys, the so-called Zerfaserungsmethode, or a teasing process, but he had been advised by Doctor Spiller, who has had a fundamental training in pathological technic, that the method is most deceptive and may lead to very misleading conclusions. Doctor Spiller called my attention to the fact that in 1901 he showed that the location of the degeneration of the spinal root by the Marchi method depends on the part of the sensory root cut. He also showed in 1910 that the tactile fibres leave the sensory root at its entrance into the pons and do not form a part of the spinal root.

But wholly apart from the criticism of the technic Van Nouhuys used in his anatomical studies, he wanted at this time to take exception to his conclusion based upon the result of the speaker's experience with subtotal section of the sensory root. Having performed the operation upon the root over 720 times, he felt entitled to an expression of opinion.

He was convinced and submitted in evidence a series of anæsthesia charts selected at random which show that if one sections the outer third of the root, one will have anæsthesia in the mandibular division; that if one sections the middle third of the root, there will be anæsthesia in the maxillary division; likewise, if one sections the inner portion of the root, there will be anæsthesia in the ophthalmic division; in any combination of these operations there will be a corresponding area of anæsthesia.

Subtotal section of the sensory root, therefore, despite Van Nouhuys' statement to the contrary, has proven an absolutely reliable procedure in that it permanently relieves the patient of pain; and, furthermore, if one leaves the ophthalmic portion of the root intact, there is no possibility of trophic keratitis as a complication. He did not see why the motor root is any more readily damaged by the temporal route than by Doctor Dandy's suboccipital route, so there is no greater danger in injuring the root.

As to the percentages of bilateral cases, Doctor Dandy's was very much higher than his. Of almost 2,000 cases of major trigeminal neuralgia which have passed through the clinic, he had knowledge all together of only some twenty cases.

With regard to facial paralysis after the operation, this has been avoided altogether by observing a simple point in the operative technic, to leave on that portion of the skull just behind the ganglion the posterior surface of the ganglion. If one makes sure to leave on this aspect of the base of the skull, just above the surface of the petrous bone, a single layer of the dura, one may always avoid injuring the trochlear nerve.

The temporal route in the hands of the majority of surgeons will be the safer of the two routes, and if it guarantees permanent relief with a hazard of 0.2 per cent., this route should be given preference.

In a recent article (ANNALS OF SURGERY, vol. xciv, pp. 1013–1017, December, 1931) Van Wagenen, an impartial observer and an experienced neurosurgeon, in conclusions as to his experience with five cases of section of the sensory root by the suboccipital route, said: "The impression is gained from these and other cases that while the operation is considerably more hazardous and difficult than through the temporal route, it is a valuable adjunct to one's neurosurgical armamentarium. No evidence has been gained from this series of cases that the type or area of anæsthesia differs from that which occurs when the trigeminal root is sectioned via the temporal fossa, provided the root is divided."

DR. WALTER E. DANDY (Baltimore): The point at which the sensory root is divided may account for the difference between the results in Doctor Frazier's operation and mine. I think unquestionably the fibers are responsible for the pain, and these particular fibers must descend into the spinal root.

It was largely the inferior results with the temporal route that led me to search for a different attack. I think it very unfair to make assertions that this approach is highly dangerous when I have done 150 such operations without a death or undesirable operative sequelæ. On the contrary, it is, in safe hands, a very safe procedure, and certainly no more dangerous than the temporal route. I think, unquestionably, the results that are obtainable by this method are much superior to those resulting from the temporal route.

If one is willing to disregard all of the advantages of the cerebellar route, the incidence of removable tumors in the posterior fossa and causing trigeminal neuralgia would alone be sufficient reason for the cerebellar instead of the temporal approach. All of these tumors would, of course, be missed if the sensory root were sectioned by the temporal route. Nor can one differentiate by clinical observations a tic due to a tumor from those in which there is no tumor.

THE INFREQUENCY OF CARCINOMA OF THE CERVIX WITH COMPLETE PROCIDENTIA

By Donald Guthrie, M.D.

and

William Bache, M.D.

of Sayre, Pa.

The interest of the senior writer in this subject was aroused by a discussion with the late John G. Clark, in 1927, just before his death, who asked him how often he had seen carcinoma of the cervix with complete procidentia. Doctor Clark, at that time, stated that in all of his experience he had never seen the two conditions associated.

We believe that the association of carcinoma of the cervix and complete procidentia is so rare that the report of a case is worthwhile, that a review of the literature on the subject and a speculation as to why the two conditions are so rarely seen associated may be of interest.

We have written to many leading gynæcologists and general surgeons wishing first to establish the rarity of the condition and to determine, if possible, why in complete procidentia carcinoma of the cervix seldom occurs, when apparently at first thought the existing conditions should be most favorable to its development.

Case No. B-20077.—J. M., married, aged fifty-three years, admitted December 26, 1929. Marital history: three pregnancies, each terminating in normal delivery, no miscarriages. Six months before admission the patient noticed a mass protruding from the vagina. A short time prior to the discovery of the protrusion she developed a bloody discharge between the menstrual periods. This bleeding began with a normal menstrual period and continued until admission. Because of the protrusion and the bleeding she had worn a tight napkin. Nine months ago she began to lose weight, in spite of a good appetite, and complained of a low backache. She developed attacks of dysuria, frequency and nocturia. She had never had the urine examined before coming to the clinic. She was a well-nourished female with an anxious expression. Heart slightly enlarged, no murmurs, no irregularities. Lungs, negative. Abdomen, negative.

Pelvic Examination.—Complete prolapse of uterus. Cervix is greatly elongated, hypertrophied, the left cervical lip is eroded, ulcerated, bleeds easily to the touch and is indurated. A foul discharge is present.

Blood-pressure.—Systolic, 165; diastolic, 110. Pulse, 84. Temperature, 99°.

Laboratory.—Blood count: hæmoglobin, 75 per cent.; red blood-cells, 4,720,000; white blood-cells, 7,000; differential, 56-44. Kahn, negative. Urine: specific gravity, 1030; alkaline, trace of albumen, 1.2 per cent. sugar, few pus cells, no red blood-cells, no casts. Blood sugar, 307 milligrams per 100 cubic centimetres of blood. Blood urea, thirty-two milligrams.

Diagnosis.—Complete procidentia, carcinoma of cervix, diabetes.

The patient was placed upon a proper diet with insulin and in twelve days she was sugar-free and in condition for operation.

January 7, 1930, operation.—Vaginal hysterectomy, Mayo type for complete prolapse.

Pathologist's Report.—Specimen consists of uterus and cervix thirteen centimetres in length. The cervix everted, ulcerated, greatly hypertrophied, measuring 5.5 centimetres in diameter. Mucous membrane is firm, dark red and slightly eroded. On section the wall of the uterus is 3.5 centimetres thick and contains considerable fibrosis. The cavity of the uterus is large and contains five polyps. The ulcerated area on the left side of the post-cervical lip extends into the cervical canal. Sections taken from this area show carcinoma epidermoid Grade III.

After a stormy and prolonged convalescence, during which time decubitus ulcers developed, the patient was discharged April 15, 1930. She returned to the hospital December 5, 1930, showing undoubted evidence of a widespread metastasis and died January 27, 1931. No autopsy was permitted.

Clinical treatises on gynæcology and surgery pay little attention to the subject. In 1882, Fritsch stated that patients with prolapse of the uterus seemed to be refractory to carcinoma of the cervix. Pomtow, in 1893, reported a case and a review of the literature at that time, finding twenty-eight cases reported in the literature. Andrews, in 1923, reported a case of a patient, aged seventy-seven years, with carcinoma and prolapse. Constantini, in 1923, reported a case, as did Nicholson in the same year. Stajano discussed the clinical differences of traumatism in the development of carcinoma of the cervix seen in prolapse.

A careful examination of the French literature shows practically no cases on record. Delvaux, in 1931, discussed the resistance of the cervix to carcinoma in total prolapse and sent out a questionnaire. In the replies from the various French surgeons he found that Hamant, of Nancy, had never seen a case. Leriche had seen but one case. Brouha had seen no cases. Foure had seen four cases, but considered it rare. Hartmann never had seen carcinomatous degeneration of the cervix with prolapse. Sebrechts had operated upon many hundreds of cases of complete prolapse and had never seen carcinoma with prolapse. Pauchet replied that true carcinoma of the cervix with procidentia is practically never seen. Backer, too, believed carcinoma of the cervix to be very rare and in the examination of 11,000 women failed to see a single case of carcinoma of the cervix with prolapse.

In 1932, Matyas reports a case of sarcoma of the cervix in a young patient of twenty-three with prolapse.

C. C. Norris (personal communication, 1930) reports that six cases were recorded in a discussion before the American Gynæcological Society a few years ago; and one or two instances were placed on record before the Philadelphia Obstetrical Society. The combined experiences of the members of these societies are enormous.

Judd, of The Mayo Clinic, reports but three cases of carcinoma of the cervix in about 2,188 cases of procidentia.

Smith, Graves and Pemberton report having seen three cases of carcinoma of the cervix in 1,000 procidentias.

In the questionnaire referred to above, reasons for the infrequent association of carcinoma of the cervix and prolapse were invited and the number of cases seen by each surgeon, or in different clinics, was requested. A brief analysis of forty-eight replies will now be given.

Twenty-eight surgeons (58.3 per cent.) reported having never seen a case, among whom were Novak, Anspach, Baldy, Vaux, Ward, Piper, Royster, Bartlett, Brent, Casler, Gellhorn, Montgomery, Müller, Maes, Keen, Hirst, Mitchell and Gardner. No cases have been seen in the Crile and Lahey clinics. It is very safe to say that the combined experience of these outstanding gynæcologists and general surgeons represents a study of many thousands of cases of procidentia. Two surgeons report finding carcinoma of the body associated with complete procidentia, but neither has seen carcinoma of the cervix with complete procidentia.

Eleven men report having seen one case, among whom are Abell, Sampson, Cullen, Richardson, Healy, Chalfant, King, Norris, Payne and Haggard.

Four men—Jeff Miller, McGlinn, the late J. O. Polak, and Taussig—report having seen two cases. Farmer has encountered the condition three times; Howard Kelly and A. H. Curtis both report having seen a very few cases.

Thirty-two surgeons (62.5 per cent.) offer no explanation for the infrequent association of carcinoma of the cervix with complete procidentia. Sixteen suggest various reasons for the rarity; less vaginal secretion and free drainage was mentioned nine times; cornification of the cervical epithelium resists the development of carcinoma was suggested nine times; the lessened area of infection in a prolapsed cervix may safeguard the patient from developing carcinoma was spoken of four times. Sixteen men mention chronic irritation and chronic ulceration of the cervix in prolapse, but do not believe it the cause of carcinomatous development. Three men suggest the usual factors which cause carcinoma, but do not mention what these factors are. One believes prolapse develops at a later time in life than that in which carcinoma of the cervix is seen; one, that the patients seek operation for carcinoma of the cervix before prolapse has taken place; another, that carcinoma of the cervix forms a fixed point and prevents prolapse occurring; one, that the carcinoma may form before the prolapse; two surgeons suggest that the absence of acid secretion may be the cause and another mentions an unknown constitutional factor.

In analyzing these various reasons why carcinoma of the cervix is seen so infrequently with procidentia, the cornified cervical epithelium becoming resistant to the development of carcinoma and less vaginal secretion, absence of infection and free drainage appear to be the commonest reasons given for the protection against carcinoma.

Smith, Graves and Pemberton, in reporting their three cases in 1,000 patients with procidentia, believe that good pelvic drainage with the absence of retained chemically changed irritating secretions plus a cornification of the epithelium of the cervix are the reasons for the infrequent associations. When the cervix is exposed to chronic irritation and dried by exposure to the air it becomes more like skin, cornified and hardened, which is not as vulnerable a tissue as some of the softer structures, as mucous membrane; only when insults are continued for a long time on an irreducible prolapse is the epithelial differentiation unable to maintain the balance of the continuous new cell formation and there results an epithelial over-growth which Waldeyer considers carcinoma to be.

In regard to free drainage, it is well to remember also, that carcinoma is more easily produced in animals by chemical irritation rather than traumatic irritation. With free drainage there is a lack of chemical irritation.

Procidentia with carcinoma of the cervix may be influenced by the age group, for carcinoma of the cervix is usually seen in relatively younger women, the older women thus have gone safely through the period when carcinoma usually develops, finally developing prolapse without carcinoma; those of the younger age may develop carcinoma of the cervix and are cured or succumb before procidentia develops; also, carcinoma of the cervix by causing fixation of the uterus may prevent the development of procidentia. It is well known that carcinoma is wont to develop at points of fixation in other organs and systems.

The ulcers seen on the irritated cervices with prolapse are more often of the decubitus type. When the prolapse is complete, there is torsion of the blood-vessels which greatly reduces circulation with resultant venous stasis. The process is very much like that seen in varicose ulcers of the leg; there is œdema, venous congestion and sclerosis of the skin, which lead to atonic ulceration, with little tendency to cicatrization. The ulcers which often ap-

pear are trophic in type. When the situation of carcinoma is considered, it is always in an area of good blood supply as well as in an area of chronic irritation. (C. H. Mayo, de Takats and Novak.)

Has the acid secretion in the vagina something to do with the development of carcinoma of the cervix? Carrell, in keeping alive malignant tissue, found that this tissue developed an acid area on its advancing margins whereas the margin about growing normal tissue, was alkaline. W. J. Mayo brings up this point and says: "Carcinoma of the stomach is common, but here again there is an acid secretion. In carcinoma of the stomach is the reduction in acidity a result of the cancer, or has it more direct relationship? Again, in the colon where cancer is frequent, the secretion, like that in the vagina, is acid as a result of bacterial action. Have the acid secretions something to do with the development of carcinoma in the presence of chronic irritation?"

One must not forget the specific diathesis of the individual patient when considering reasons for the development of carcinoma in any given case; there should be a hereditary factor together with the proper kind and amount of irritation at the proper time. In many of the cases conditions favorable for the presence of carcinoma of the cervix were present in the form of laceration from childbirth and infections, the carcinoma developing after the prolapse. Would carcinoma have developed in some of these patients had procidentia not occurred?

The number of cases reported is too great for the rarity to be used as an argument against the irritation theory entirely; on the other hand, no matter how great the irritation to which the prolapsed cervix is exposed by rubbing of the clothing, the thighs, tight supporting pads, irritation from urine, carcinoma of the cervix probably does not occur without a hereditary predisposition on the part of the patient.

Delvaux pleads for a systematic investigation of this mysterious immunity of the cervix to carcinoma in the presence of procidentia and believes, strongly, that as a result of such an investigation, there would be a great advance in the discovery of the etiology of cancer.

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DISCUSSION.—DR. F. N. G. STARR (Toronto) recalled an elderly woman of seventy-five whom he saw years ago. After she had had a procidentia for some thirty years she began to have bleeding. At first she thought she was renewing her youth but when the bleeding persisted and the foul discharge occurred, she sought some relief. Doctor Starr found she had a carcinoma and did a vaginal hysterectomy. He promised her he would drink a cup of tea with her on her eighty-fifth birthday, and that came off just about a year ago.

DR. JAMES C. MASSON (Rochester, Minn.) said he had operated on several cases with extensive prolapse, with extensive ulceration, and in many of these cases the patients thought they had malignancy, and their attending physician had thought malignancy existed, but in his own experience he had never operated on a patient with complete prolapse of the uterus in which cancer of the cervix existed. He considered the age factor as the most important consideration. The majority of women who develop malignancy of the cervix develop it close to the menopause time. At that age, he said, we see very few patients with complete procidentia. Later on, after the menopause, on account of the atrophy associated at that time, if there is a tendency to prolapse, the uterus rapidly sinks to a lower level. That is the time these women consult a surgeon for procidentia. The acid secretion of the vagina probably is a factor predisposing to cancer of the cervix and when the cervix protrudes beyond the vulva, this cause is eliminated.

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Philadelphia, Penna.